The role of vitamin D in melanogenesis with an emphasis on vitiligo

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ABSTRACT

Vitiligo is a common pigmentary disorder caused by the destruction of functional melanocytes. Vitamin D is an essential hormone synthesized in the skin and is responsible for skin pigmentation. Low levels of vitamin D have been observed in vitiligo patients and in patients with other autoimmune diseases. Therefore, the relationship between vitamin D and vitiligo needs to be investigated more thoroughly. We reviewed the literature to date regarding the role of vitamin D in skin pigmentation. Our review revealed that vitamin D deficiency has been identified in many conditions, including premature and dysmature birth, pigmented skin, obesity, advanced age, and malabsorption. Vitamin D increases melanogenesis and the tyrosinase content of cultured human melanocytes by its antiapoptotic effect. However, a few growth-inhibitory effects on melanocytes were also reported. Vitamin D regulates calcium and bone metabolism, controls cell proliferation and differentiation, and exerts immunoregulatory activities. Vitamin D exerts its effect via a nuclear hormone receptor for vitamin D. The topical application of vitamin D increased the number of L-3,4-dihydroxyphenylalanine-positive melanocytes. The topical application of vitamin D yields significant results when used in combination with phototherapy and ultraviolet exposure to treat vitiligo in humans. Vitamin D decreases the expression of various cytokines that cause vitiligo. In conclusion, application of vitamin D might help in preventing destruction of melanocytes thus causing vitiligo and other autoimmune disorders. The association between low vitamin D levels and the occurrence of vitiligo and other forms of autoimmunity is to be further evaluated.

Key words: Autoimmune diseases, depigmentation, melanocytes, phototherapy, vitamin D, vitamin D receptor, vitiligo

INTRODUCTION

Vitiligo is a common pigmentary disorder characterized by well-demarcated depigmented patches or macules of different shapes and sizes. Vitiligo is caused by the destruction of functional melanocytes in the involved epidermis and the bulb/infundibulum of the hair follicle.[1-3] Vitiligo is an autoimmune disorder that affects 1-4% of the world’s population,[4] regardless of gender or basic skin tone.[5] The disorder results in substantial cosmetic disfigurement. In some cultures, patients with vitiligo are regarded as social outcasts and are emotionally and physically affected.[3]

A variety of therapeutic agents have been described in the literature, and many agents have been used in an attempt to treat vitiligo. However, no agent has been found to be uniformly effective. The most widely prescribed therapies are phototherapy and topical corticosteroids.[1,6]

The active form of vitamin D, calcitriol [1,25-dihydroxyvitamin D3, 1,25(OH)2D3], and analogues of this hormone (e.g., calcipotriol) are successful treatment options for patients with skin diseases, such as psoriasis and vitiligo,[7] when used topically.
Although the association between vitamin D and pigmentation and the role of vitamin D deficiency has been established in numerous autoimmune diseases, the association between vitamin D levels and vitiligo still needs to be investigated more thoroughly. In this review, we summarize the existing information on the relationship between vitamin D, autoimmune diseases and pigmentation; we also highlight the knowledge gaps concerning the relationship between vitamin D and vitiligo.

In this review, we aimed to systematically review the published scientific literature till date regarding the role of vitamin D to enhance the pigmentation in human skin. We searched databases including MEDLINE/Pubmed, Embase, and Google Scholar for vitiligo, vitamin D, autoimmune diseases, melanocytes, vitamin D receptor, phototherapy, and depigmentation.

**BASIC SCIENCE OF VITAMIN D**

**Vitamin D**
Vitamin D is an essential hormone that is synthesized in the skin via a photochemical reaction, following the exposure of the skin to ultraviolet B (UVB) wavelength present in sunlight. In this reaction, previtamin D is converted by solar UVB-radiation in the skin into vitamin D, especially during the summer months. Limitations of vitamin D synthesis are age, pigmented skin, sunscreen use, and clothing. Skin pigmentation is a known risk factor in patients with hypovitaminosis D because melanin, which is responsible for skin pigmentation, filters UV-radiation.

**Vitamin D derivatives**
The two main forms of vitamin D are cholecalciferol and ergocalciferol. Both forms of vitamin D can be obtained by nutritional intake; ergocalciferol (vitamin D₂) is present in fungi/yeast, whereas cholecalciferol (vitamin D₃) is found in foods from animal origin, especially fatty fish, such as herring and mackerel. Other sources of vitamin D are milk, cheese, eggs, and cereals.

**Biochemistry of vitamin D**
The active form of vitamin D, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], is a secosteroid (steroid with an opened B-ring) hormone that regulates calcium and bone metabolism, controls cell proliferation and differentiation and exerts immunoregulatory activities. This range of functions has been exploited clinically to treat a variety of conditions, including secondary hyperparathyroidism, osteoporosis, psoriasis, and vitiligo. Recent advances in the understanding of 1,25(OH)₂D₃ and its functions and novel insights into the mechanisms of its immunomodulatory properties suggest a wider applicability of this hormone in the treatment of autoimmune diseases and the prevention of allograft rejection.

**Physiology of vitamin D**
The primary form of vitamin D, cholecalciferol [25(OH)D₃, the form measured to determine the level of vitamin D], is synthesized in the liver. The biologically active form, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], is then synthesized in the kidneys via the hydroxylation of 25(OH)D₃ by 1α-hydroxylase and stimulates calcium absorption from the gut. The target organs of 1,25(OH)₂D₃ include the bone, intestine, and kidney and it stimulates calcium transport from these organs to the blood. The production of 1,25(OH)₂D₃ is stimulated by the parathyroid hormone (PTH). There is a negative feedback through calcium that decreases PTH and a direct negative feedback from 1,25(OH)₂D₃ to PTH. The active metabolite 1,25(OH)₂D₃ also shows rapid activities through a membrane receptor.

**Vitamin D receptor**
Vitamin D exerts its effect via a nuclear hormone receptor called the vitamin D receptor (VDR). VDR is a member of the superfamily of nuclear receptors for steroid hormones, thyroid hormone, and retinoic acid. The VDR is a type 1 nuclear receptor, a transcription factor that forms homodimers and heterodimers that are active in the transcription and transrepression of approximately 900 genes. VDRs are present not only in cells typically involved in calcium and bone metabolism but also in other cell types, such as keratinocytes, melanocytes, fibroblasts, and immune-system cells of the skin. VDR acts by binding to specific DNA sequences as a heterodimer with a retinoid X receptor and to the basal transcription machinery in a ligand-independent (TFIIB) and -dependent manner (TFIIA). Genes with vitamin D response elements directly and indirectly influence cell cycling and proliferation, differentiation, and apoptosis.

Birlea et al., found an association between the VDR-ApaI polymorphism and vitiligo. This study revealed that aa genotype of Apa-I VDR was significantly more
frequent in patients with vitiligo; allelic frequencies showed a significant difference between vitiligo with other autoimmune diseases group and controls. VDR gene polymorphisms may affect 25(OH) D levels and the risk for the development of vitiligo. The VDR variant BsmI-B allele, the ApaI-A allele, and the TaqI-t allele were associated with a decreased risk for vitiligo, and there was also a dose-response relationship between decreased risk and increased 25(OH) D level in individuals with the ApaI allele.[19] In another study, Aydingoz et al., concluded that VDR TaqI gene polymorphism and the haplotype BsmI/ApaI/TaqI/FokI/Cdx2 GCCCG may be considered as novel risk factors in vitiligo.[20]

VITILIGO, CLINICAL DISORDERS, AND VITAMIN D

Vitamin D deficiency and diseases
Risk factors for vitamin D deficiency are premature and dysmature birth, pigmented skin, low sunshine exposure, obesity, advanced age, and malabsorption. The prevalence of vitamin D deficiency is also higher in elderly people than in adults, and it is especially prevalent in patients with hip fractures and in the residents of homes for the elderly and nursing homes.[21] The low vitamin D levels found in Pemphigus vulgaris and Bullous pemphigoid may suggest a role for this agent in their pathogenesis. The prevalence of fracture was increased in this group.[22] Low levels of vitamin D have also been associated with cardiovascular disease, including myocardial infarction.[23]

The prevalence of vitamin D deficiency is much higher in Europe than in Asia, Australia, or the USA. The prevalence of vitamin D insufficiency is also high in African Americans, whose highly pigmented skin makes the UV-light much less efficacious.[24] A high prevalence of vitamin D deficiency has been reported in nonwestern immigrants in the Netherlands,[25] and similar data was obtained in the Middle East,[26] where life-style factors probably play a role.

Black patients have a higher risk of insufficiency of vitamin D than White patients, and it was observed that prepubescent White girls have higher vitamin D levels than Black girls in the United States.[27] It has been reported that lower vitamin D levels in patients of color may explain the increased rates of peripheral vascular disease and invasive breast cancer.[28] VDR polymorphisms have been associated with breast cancer cases in Caucasian females, but not in African-American females, suggesting that chronic low levels of vitamin D are more at fault.[29]

Low vitamin D levels have also been associated with autoimmune diseases, including systemic lupus, diabetes mellitus, rheumatoid arthritis, and multiple sclerosis.[30-33] The mechanism by which vitamin D affects autoimmunity is unknown, but there is a clear regulation of immune cells by vitamin D in vitro.[30] The association of low vitamin D levels with vitiligo and multiple forms of autoimmunity needs to be further evaluated.

IN VITRO STUDIES

Murine B16 melanoma cells treated with vitamin D₃ exhibit an increase in tyrosinase activity and melanogenesis.[34] Tomita et al., showed that vitamin D₃ increased the tyrosinase content of cultured human melanocytes.[35] Watabe et al., provided some important clues to understand the role of vitamin D₃ in melanocyte development and melanogenesis and observed that L-3,4-dihydroxyphenylalanine-positive (DOPA-positive) cells are increased after 1,25(OH)₂D₃ treatment in primary neural crest cell cultures.[36] These findings indicate that 1,25(OH)₂D₃ may stimulate the differentiation of immature melanocyte precursors. Electron microscopy demonstrates the presence of melanosomes at more advanced stages in 1,25(OH)₂D₃-treated cells as compared with untreated cells.[36] In another study, it was observed that vitamin D and UVB irradiation promoted the proliferation of melanocytes, which indicates that this combination might be effective in the treatment of vitiligo.[37]

GROWTH INHIBITORY EFFECTS OF VITAMIN D ON MELANOCYTES

In contrast to its stimulatory effects on melanocyte proliferation, vitamin D was also reported to have an inhibitory effect on melanocyte growth[38] as well as the melanization of cultured human melanocytes.[39] In another study, vitamin D inhibited the proliferation of melanocytes in a dose-dependent manner, though it did not show any adverse effects on the melanization process of melanocytes.[40]

IN VIVO STUDIES

Abdel-Malek et al., showed that the topical application of 100 μg of cholecalciferol to the pinnal epidermis of
DBA/2J mice for 5 or 10 days increased the number of DOPA-positive melanocytes and had a synergistic effect with a low dose of UVB-light. The combination of psoralen and ultraviolet A (PUVA) with calcipotriol in vitiligo works fast, and the duration of PUVA treatment can be reduced to yield more cosmetically acceptable results.

**VITAMIN D AND VITILIGO**

Topical vitamin D3 analogues are a new addition to the armamentarium of therapeutic modalities for vitiligo. The use of vitamin D analogues in combination with PUVA sol and topical calcipotriol for the treatment of vitiligo was first reported by Parsad et al. Subsequently, a number of studies have been reported the treatment of vitiligo with vitamin D analogues alone or in combination with ultraviolet light or corticosteroids to enhance repigmentation. In a recent review, Birlea et al., have shown insight into the main intracellular pathways through which vitamin D3 analogues alone or in different combinations may contribute to repigmentation in vitiligo. Birlea et al., reviewed 22 studies published on calcipotriol/tacalcitol used alone or in combination with other agents for evaluation and concluded that many studies have shown vitamin D3 analogues to be effective in combination with PUVA, NBUVB, or an excimer laser. In another study, Oh et al., reported that high concentration of tacalcitol was applied topically with 308-nm xenon chloride excimer laser to lower the energy threshold for significant clinical purpose to treat nonsegmental vitiligo.

In a recent pilot study, serum concentrations of vitamin D in vitiligo patients were estimated and divided into three groups: 31.1% were normal (>30 ng/mL), 55.6% were insufficient (<30 ng/mL), and 13.3% were very low (<15 ng/mL). Insufficient vitamin D levels were associated with an increasing Fitzpatrick phototype. Very low 25-hydroxyvitamin D levels were associated with comorbid autoimmune illnesses, but not with age, gender, race/ethnicity, family history of vitiligo or autoimmune disease, new-onset disease, or body surface area affected. This study was limited, as it assessed point prevalence in a small cohort (total of 45 patients) without assessing the seasonal variations in vitamin D levels and as there was no control group. In a recently published case report, investigators found low levels of vitamin D (12 ng/mL) in a vitiligo patient.

Another study investigated the association between VDR polymorphisms and vitiligo, and it revealed that the Apa-I polymorphism of the VDR gene is associated with vitiligo. This suggests that vitamin D or its receptor might play a role in the etiopathogenesis of skin pigmentation.

**VITILIGO TREATMENT AND VITAMIN D**

Application of vitamin D with phototherapy and UV exposure to treat vitiligo

The occurrence of hyper-pigmentation in psoriatic lesions treated with calcipotriol led to the discovery of a new therapeutic modality in vitiligo. Calcipotriol is effective on immunomodulatory systems, inflammatory mediators, and melanocytes and it may stimulate melanin production by activating melanocytes and keratinocytes. It has been found in vivo that melanocytes in the epidermis become swollen with elongated dendrites after UV-irradiation of the skin. The tyrosinase activity in these melanocytes is increased by microphthalmia transcription factor (MITF), resulting in the deposition of the enzyme product, melanin, in the epidermis, several days after irradiation. Tomita et al., found that vitamin D3-induced features similar to those noted in UV-irradiated skin; specifically, it increased the cell size, the number of dendrites, and the amount of immunoreactive tyrosinase. Ermis et al., also reported that combination treatment with calcipotriol and PUVA seems to be safe and much more effective in initiating and achieving complete repigmentation than a placebo with PUVA.

A marginal type of repigmentation pattern occurred more frequently with these topical agents, and it was observed that the onset of repigmentation induced by calcipotriol was slow. However, in a few cases, treatment failure or no added response to combination therapy with these analogues was also observed at the end of 3 months.

**INFLUENCE OF NARROWBAND UVB PHOTOTHERAPY ON VITAMIN D**

A recent study investigated the influence of low-dose narrowband UVB phototherapy on serum levels of vitamin D. The results of the study revealed that UVB phototherapy increased vitamin D levels in patients with low initial levels of 25-hydroxyvitamin D (25(OH) D) (the serum marker for vitamin D status),
which indicates that the beneficial effect of UVB depends, at least partially, on the induction of vitamin D.

**VITAMIN D REGULATES CA\(^{2+}\) FOR PIGMENTATION**

Defective calcium (Ca\(^{2+}\)) transport has been shown in keratinocytes and melanocytes obtained from vitiliginous skin samples.\[^{53}\] Ca\(^{2+}\) controls the activity of both plasma membrane-associated and cytosolic thioredoxin reductase. Decreased intracellular Ca\(^{2+}\) leads to high levels of reduced thioredoxin, the product of thioredoxin, which inhibits tyrosinase activity and results in the inhibition of melanin synthesis. Moreover, it has been shown that melanocytes express 1,25-dihydroxyvitamin D\(_3\) receptors, which take part in the regulation of melanin synthesis.\[^{41,54}\] It is likely that calcipotriol may play a role in Ca\(^{2+}\) regulation by 1,25-dihydroxyvitamin D\(_3\) receptors on melanocytes and/or by the regulation of defective Ca\(^{2+}\) homeostasis.\[^{50}\]

**EFFECTS OF VITAMIN D ON VITILIGO BY DECREASING THE EXPRESSION OF CYTOKINES**

It has been reported that the increased expression of proinflammatory and proapoptotic cytokines, such as IL-6, IL-8, IL-10, IL-12, INF-\(\alpha\), and TNF-\(\alpha\), cause vitiligo and play a role in the pathogenesis of vitiligo.\[^{2,55}\] Vitamin D might exert immunomodulatory effects by inhibiting the expression of IL-6, IL-8, TNF-\(\alpha\), and TNF-\(\gamma\).\[^{56}\] Vitamin D compounds were shown to have modulatory effects on dendritic cell maturation, differentiation, and activation in both human and murine culture systems,\[^{57}\] probably via a VDR-dependent pathway.\[^{58}\] Furthermore, vitamin D compounds are shown to induce the inhibition of antigen presentation.\[^{57,58}\]

**EFFECTS OF ORAL VITAMIN D SUPPLEMENTS ON AUTOIMMUNE DISEASES**

In many studies, it was observed that vitamin D supplementation was therapeutically effective in different experimental animal models, such as allergic encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis, and systemic lupus erythematosus.\[^{59-63}\] Therefore, the supplementation of vitamin D can possibly be used as a treatment in autoimmune diseases such as vitiligo.

**MOLECULAR MECHANISM OF REPIGMENTATION BY VITAMIN D**

Vitamin D protects the epidermal melanin unit and restores melanocyte integrity by two main mechanisms: By controlling the activation, proliferation, migration of melanocytes and pigmentation pathways by modulating T cell activation, which is apparently correlated with melanocyte disappearance in vitiligo. The multiple effects of VDR on immune cells lead to the recognition that vitamin D could be a potent immunomodulator. The coordination of T cell activation is exerted mainly by the inhibition of T cell transition from the early to the late G1 phase and by the inhibition of several cytokine genes, such as those encoding TNF-\(\alpha\) and IFN-\(\gamma\).\[^{64}\]

The mechanism through which vitamin D exerts its effects on melanocytes is not yet fully understood. Vitamin D is believed to be involved in melanocyte physiology by coordinating melanogenic cytokines [most likely endothelin-3 (ET-3)] and the activity of the SCF/c-Kit system, which is one of the most important regulators of melanocyte viability and maturation.\[^{64}\] Furthermore, a proposed mechanism involving vitamin D in the protection of vitiliginous skin is based on its antioxidant properties and regulatory function towards the reactive oxygen species that are produced in excess in vitiligo epidermis.

**VITAMIN D REDUCES APOPTOTIC ACTIVITY IN MELANOCYTES**

Vitiligo is characterized by the loss of melanocytes from the epidermis, which causes depigmentation in the skin.\[^{65}\] Apoptosis has been reported to be a mechanism that removes melanocytes from the skin.\[^{66}\] The active form of vitamin D reduces the apoptotic activity induced by UVB in keratinocytes\[^{67}\] and melanocytes\[^{68}\] by the production of interleukin-6.\[^{67}\] In another study, it was observed that vitamin D protected melanocytes from apoptosis through the formation of sphingosine-1-phosphate [Table 1], which opposes apoptotic action in diverse melanoma cell lines.\[^{69}\] A recent study reported that vitamin D protects DNA against oxidative damage, with net tumoristic and anticarcinogenic effects.\[^{70}\] The mentioned studies provide evidence that vitamin D can prevent the death of melanocytes, thus preventing the loss of pigment in the skin, which could be a very useful finding in the treatment of vitiligo, if approached correctly.
There are a few important steps that should be followed during the treatment of vitiligo with vitamin D in the clinic. The first step is the selection of patients, as variation in patient features, such as age or duration, extent and type of vitiligo, and affected areas, are important considerations in determining the applicability of treatment and may result in variable responses. As the mechanism of vitamin D action is slow, vitamin D analogues will be effective in patients with stable disease or slow-spreading disease. The second step is to measure the vitiligo affected area by a standard method before and after treatment, as it is an important limiting factor and there is no uniformly accepted scoring system for disease activity. Recently, our group reviewed different vitiligo assessment methods to assess the depigmented and pigmented areas in vitiligo patients before and after treatment.[71]

### CONCLUSIONS AND FUTURE DIRECTIONS

Vitiligo is caused by the destruction of functional melanocytes in the epidermis. Vitiligo is generally considered to be an autoimmune disorder. There is preliminary evidence that vitiligo patients, as well as patients with other autoimmune disorders have low levels of vitamin D. Vitamin D is synthesized in the skin in the presence of UVB wavelengths that come from sunlight. Vitamin D and its analogues have been used to successfully treat vitiligo and psoriasis. Vitamin D efficiency is increased when used in combination with UV or corticosteroids. However, in a few in vitro studies, vitamin D showed inhibitory effects on the growth of melanocytes, while in some cases, it was not effective for repigmentation. Other effects of vitamin D on melanocytes are summarized in Table 1.

It is still unknown if vitamin D deficiency plays a role in causing vitiligo, as it does in other autoimmune diseases. If vitamin D deficiency does cause vitiligo, then its supplementation could help control the disease. Therefore, the relationship between the level of serum vitamin D and vitiligo should be tested in a large controlled study. Moreover, oral vitamin D intake should be observed to prevent disease onset in susceptible family members of vitiligo patients. More studies are to be performed on this topic to reveal the effect of phototherapy and the application of vitamin D on repigmentation. Additionally, more studies are necessary to determine the association of VDR polymorphisms and disease activity in vitiligo patients.

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### REFERENCES


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### Table 1: Response of Vitamin D on melanocytes and skin repigmentation

<table>
<thead>
<tr>
<th>Action of vitamin D</th>
<th>Response</th>
<th>References</th>
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<tbody>
<tr>
<td>Vitamin D</td>
<td>It acts on specific T cell by inhibiting the expression of several proinflammatory cytokines genes, such as tumor necrosis factor alpha and interferon gamma in vitiligo</td>
<td>Birlea et al.[84]</td>
</tr>
<tr>
<td>1alpha, 25-Dihydrovitamin D3</td>
<td>It protects human melanocytes from apoptosis by formation of sphingosine-1-phosphate</td>
<td>Sauer et al.[84]</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D3 [1,25(OH) 2D3]</td>
<td>It has antiapoptotic effects and decreased cyclobutane pyrimidine dimers damage by up to 60%</td>
<td>Wong et al.[72]</td>
</tr>
<tr>
<td>Tacalcitol, a vitamin D analogue</td>
<td>Tacalcitol plays a role in Ca(^{2+}) regulation by vitamin D receptor (VDR) on melanocytes</td>
<td>Lu-yan[73]</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>VDR is the nuclear receptor that mediates the effects of vitamin D through regulating the transcription of other genes</td>
<td>Han et al.[74]</td>
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</table>


Multiple choice questions

1. Vitamin D is synthesized in the skin in the presence of
   a. Ultraviolet B
   b. Red light
   c. Green light
   d. Infra-red light

2. The source of ergocalciferol (vitamin D2)
   a. Bacteria
   b. Fungi/yeast
   c. Algae
   d. Lichens

3. The active form of vitamin D (1,25-dihydroxyvitamin D3) regulates metabolism of
   a. Calcium
   b. Iron
   c. Fluoride
   d. Phosphate

4. The primary form of vitamin D (cholecalciferol) is synthesized in the
   a. Pancreas
   b. Gall bladder
   c. Intestine
   d. Liver

5. The production of vitamin D (1,25(OH)2D3) is stimulated by
   a. Gonadotropin
   b. Luteinizing hormone
   c. Parathyroid hormone
   d. Testosterone

6. What is the normal level of vitamin D in serum?
   a. >30 ng/mL
   b. from 15 to 30 ng/mL
   c. <15 ng/mL
   d. <5 ng/mL
7. Which type of radiation is filtered by melanin?
   a. Visible radiation   b. Ultraviolet radiation
   c. Electromagnetic radiation   d. Infrared radiation

8. Vitamin D receptor is a member of the superfamily of nuclear receptors for
   a. Adrenal hormones   b. Gonadotropin hormones
   c. Luteinizing hormones   d. Steroid hormones

9. Vitamin D protects melanocytes from apoptosis through the formation of
   a. Sphingosine-1-carbonate   b. Sphingosine-1-oxolate
   c. Sphingosine-1-phosphate   d. Sphingosine-1-fluorate

10. The active form of vitamin D reduces the apoptotic activity in melanocytes by the production of
    a. Interleukin-6   b. Interleukin-8
     c. Interleukin-10   d. Interleukin-12
Acitretin in dermatology

Rashmi Sarkar, Shikha Chugh, Vijay K. Garg

ABSTRACT

Acitretin, a synthetic retinoid has gradually replaced etretinate in today’s dermatologic practice because of its more favorable pharmacokinetics. Acitretin over the past 20 years has proven useful in a number of difficult-to-treat hyperkeratotic and inflammatory dermatoses and nonmelanoma skin cancers. It is effective both as monotherapy and in combination with other drugs for hyperkeratotic disorders. It is considered to be an established second line treatment for psoriasis and exerts its effect mainly due to its antikeratinizing, antiinflammatory, and antiproliferative effect. Its antineoplastic properties make it a useful agent for cancer prophylaxis. Evidence-based efficacy, side-effect profile, and approach to the use of acitretin would be discussed in this review. In addition to its approved uses, the various off label uses will also be highlighted in this section. Since its use is limited by its teratogenic potential and other adverse effects, including mucocutaneous effects and hepatotoxicity, this review would summarize the contraindications and precautions to be exercised before prescribing acitretin.

Key words: Acitretin, chemoprevention, psoriasis

INTRODUCTION

The skin absorbs, stores, and metabolizes vitamin A. Retinoids influence cellular division and differentiation of stratified structures of the epidermis. Many of the physiological responses of the skin, such as dermal aging, immune defense, and wound healing are significantly affected by retinoids. Interest in the effects of retinol, retinyl palmitate, and other retinoids on skin is a subject for continued investigation. Synthetic retinoids are classified into three generations including nonaromatic, monoaromatic, and polyaromatic compounds.

- First generation retinoids: Which include retinol, retinal, tretinoin (retinoic acid, Retin-A), isotretinoin, and alitretinoin.
- Second generation retinoids: Which include etretinate and acitretin.
- Third generation retinoids: Which include tazarotene, bexarotene, and adapalene.

Acitretin, a synthetic retinoid, is the pharmacologically active metabolite of etretinate. The aromatic retinoids (second generation) were developed because they appeared to be more effective in treating psoriasis and other keratinizing disorders. In 1986, etretinate was approved for the treatment of psoriasis, but problems like long-term storage in fat led to its replacement with acitretin in 1998. With its more favorable pharmacokinetics (acitretin being 50 times less lipophilic than etretinate has significantly shorter elimination half-life), acitretin became an established systemic therapy for severe psoriasis.

PHARMACOKINETICS

Acitretin is rapidly and extensively distributed throughout the body bound to plasma proteins without tissue accumulation. It is metabolized mainly in the liver into 13-cisisoacitretin, which is excreted both in urine and feces.[1-3] Its bioavailability is increased by intake with fatty food.[4] As studied in human hepatocyte cultures, alcohol indirectly increases the conversion of acitretin to etretinate by...
acting as a catalyst for hepatic enzymes, a process known as reverse esterification.\[^{1,5}\] The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined and whether substances other than ethanol are associated with transesterification is not clear. In a study by Gronhoj et al., on 86 patients on acitretin, a trend linking higher risk of etretinate formation with higher dose of alcohol consumption was found (all 16 patients with average >200 g/week alcohol intake having detectable etretinate). As etretinate is more lipid-soluble and has longer T1/2, it is especially important for pregnant females to avoid alcohol intake during pregnancy and for 2 months after discontinuation of acitretin therapy.

MECHANISM OF ACTION

Acitretin acts at cytosolic proteins and intranuclear receptors, which are part of the steroid–thyroid hormone super family. The metabolites of acitretin bind to retinoic acid receptors (RARs), which lead to alteration of gene transcription through response elements, leading to antiproliferative and antiinflammatory effects. In psoriasis and other disorders of keratinization, acitretin normalizes epidermal cell proliferation, differentiation, and cornification.\[^{2,3,6,7}\]

A. Acitretin stimulates differentiation and normalizes accelerated epidermopoiesis of pathological epidermis

B. It decreases release of leucotrienes and dihydroeicosatetraenoic acid products and inhibits neutrophil chemotaxis into the epidermis. It also interferes with the esterification and incorporation of arachidonic acid into nonphosphorus lipids in human keratinocytes and causes inhibition of ornithine decarboxylase thus decreasing the synthesis of polyamines. It also inhibits keratinocyte production of vascular endothelial growth factor.

C. It inhibits cell growth and proliferation and decreases AMP-dependent protein kinases in fibroblasts.

1. Antineoplastic effects: By normalizing abnormal epidermopoiesis acitretin exerts its anticarcinogenic effects. It also inhibits tumor cell angiogenesis and modulates cellular apoptosis. Retinoids influence growth factors, can indirectly down-regulate proto-oncogenes and may act to increase intracellular levels of ceramides. These changes may lead to decrease in cell growth and possibly inhibit malignant progression

2. Wound healing: Retinoids lead to increased mucopolysaccharides, collagen, and fibronectin synthesis and decrease in collagenase production interfere with wound healing

3. Antiacne and sebum effects: Caused by inhibition of sebocyte proliferation although the potency of acitretin (27.5%) is much lower than isotretinoin (48.2%).

USES

Psoriasis

The effect is dose dependant. A total of seven studies, (level of evidence of 3), showed partial remission (PASI 75) in 25-75% of the patients, in doses of 30-40 mg daily.\[^{7-11}\] In a study by Gupta et al. with 24 patients, daily treatment with acitretin 10 or 25 mg did not lead to any improvement in skin lesions, whereas daily doses of 50 and 75 mg resulted in an improvement of at least 75% in 25% of the patients with psoriasis.\[^{12}\] Acitretin is licensed for use in severe extensive psoriasis, which is resistant to other forms of therapy, including topical, light and systemic and palmoplantar pustular psoriasis.\[^{13}\] An initial worsening of psoriasis symptoms is sometimes seen at the beginning of the treatment period.

1. Generalized pustular psoriasis: In a study on 385 patients of generalized pustular psoriasis retinoid therapy was effective in 84% of patients, methotrexate in 76%, and cyclosporine in 71%, making retinoids the choice of drug in generalized pustular psoriasis.\[^{14}\]

2. Palmoplantar pustulosis: In two randomized controlled trials (RCTs) Expand comparing acitretin with placebo in palmoplantar pustulosis, acitretin was significantly more effective than placebo, acting within 4 weeks to produce a 5-fold reduction in pustules.\[^{15}\] In the study by Lassus and Geiger, comparing acitretin and etretinate there was a 10-fold reduction in pustules after 12 weeks of therapy, however, the difference in the efficacy of two drugs was not significant.\[^{14}\]

3. Erythrodermic psoriasis: As monotherapy, acitretin has been shown to be effective in treating erythrodermic psoriasis.

4. Severe plaque type psoriasis: The efficacy of acitretin in chronic plaque psoriasis
as a monotherapy is below methotrexate and cyclosporine. However, when used in combination with other topical and systemic therapies (topical corticosteroids, topical vitamin D preparations, psoralen with UVA (PUVA, ultraviolet B (UVB) therapy) it is as potent as classical therapies.

5. Nail psoriasis: In an open study of 396 patients with nail psoriasis who received acitretin in doses of 0.2-0.3 mg/kg daily for 6 months, the mean improvement in Nail Psoriasis Severity Index was 41% and 25% of patients cleared completely or almost cleared.[16]

6. Psoriasis associated with human immunodeficiency virus (HIV) infection: Acitretin is the only drug in antipsoriatic armarium that does not appear to have immunosuppressive properties and hence can be used even in HIV and immunosuppressed patients.

In a retrospective analysis of eight RCTs comparing acitretin with placebo and acitretin with etretinate, in patients with generalized pustular, severe and erythrodermic psoriasis patients, the results were heterogeneous, acitretin was found to be effective as compared with placebo with effect being dose dependant (50-75 mg daily more effective than low dose).[13] Acitretin in doses of 10-25 mg daily was not significantly better than placebo. However, the study period was short and longer-term open extensions with variable doses titrated to the patients’ needs suggest greater efficacy over time with reduction in area and increasing percentage of patients clearing between 20 and 52 weeks. Typically 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75) was seen at 12 weeks in most of the studies.

A recent systematic review of efficacy of oral retinoids as single agent or combined therapy in plaque-type psoriasis (PV), nail psoriasis and localized and generalized pustular psoriasis: Initial and optimal dosage; was compiled by Sbidian et al.[17] Out of the 44 RCTs studied in most of the studies, starting daily dosages were between 10 and 25 mg and stepwise escalation was associated with higher clinical efficacy and lower incidence of adverse events in comparison with higher doses and regimens rapidly reaching optimal dose. Retinoids as single agent therapy appeared to show limited efficacy in PV, whereas good clinical efficacy was reported in pustular forms, which may, however, spontaneously remit. Retinoids in combination with phototherapy were highly effective.

In the comparative studies with etretinate there was a trend for acitretin to be slightly less effective and to present a higher incidence of similar side-effects. In an 8-week trial in 175 patients acitretin at 10, 25, and 50 mg daily produced a 50% improvement in psoriasis in 50%, 40.5%, and 54%, respectively, compared with 61% with etretinate.[18] Side-effects, like efficacy, were dose related as found by Pearce et al., where common adverse events (deranged liver enzymes and lipid profile) were two to three times more frequent in patients receiving 50 mg daily compared with patients receiving 25 mg daily.[19]

Optimal dosing

In a randomized double-blind study by Dogra et al., 61 patients of severe plaque psoriasis were divided into three groups to receive acitretin in doses of 25, 35, and 50 mg per day for 12 weeks. After 12 weeks the percentage reduction in the PASI score was 54%, 76%, and 54% and PASI 75 was achieved in 47%, 69%, and 53% patients in 25, 35, and 50 acitretin mg/day groups, respectively. The majority of adverse events were mucocutaneous, mild-to-moderate severity, and dose dependent. Thus 35 mg dosing appeared to be most efficacious and safe for psoriasis patients.[20]

There is evidence to support that low doses of acitretin has reduced adverse events but still maintains efficacy. Retrospective analysis of data from two large randomized trials, which had an 8-week, double-blinded (DB), placebo-controlled phase followed by a 16-week open-label (OL) phase was done by Haushalter et al.[21] During the DB phase, patients received placebo, 10, 25, 50, or 75 mg of acitretin daily. During the OL phase, patients received either high-dose treatment of approximately 50 mg/day or low-dose of 25 mg/day. At the end of the OL phase (24 weeks), treatment success rates were similar among all groups (29-33%) with highest rates in the group receiving low-dose treatment for both DB and OL phases (47% success). Decrease in bovine serum albumin (BSA) was also highest in this group (73% vs. 28-54%). Thus, individualization of acitretin dosing is crucial to minimize side effects and improving adherence and efficacy. This analysis supports the utility of low-dose acitretin for psoriasis over extended treatment periods.

COMBINATION THERAPY

Acitretin and PUVA: The major advantage of this combination is reduced risk of malignancy by phototherapy especially squamous cell carcinoma.
Four RCTs compared acitretin and PUVA (rePUVA) with placebo and PUVA, and showed acitretin-PUVA combination to be more effective than PUVA alone, reducing the number of PUVA treatments, exposure to UVA and the clinical scores.[11,13] In a randomized, double-blind comparative study of 48 patients with severe, widespread psoriasis treated either with photochemotherapy (PUVA) alone or combination with acitretin, marked or complete clearing of psoriasis occurred in 80% of the patients (20 of 25) without acitretin and in 96% of the patients (22 of 23) with adjunctive acitretin administration. The mean cumulative UVA dose given to patients in the acitretin-PUVA group was 42% less than that required for patients in the placebo-PUVA group.

Acitretin and ultraviolet B
Studies comparing acitretin in combination with UVB versus UVB alone found better outcomes and sparing of UVB with acitretin-UVB in combination than with UVB alone.[13] Clearance occurred in 89% treated with acitretin-UVB (ReUVB) versus (62.5%) patients given UVB alone. The improvement score was significantly higher for the ReUVB side than the acitretin side. Patients treated with ReUVB showed a statistically higher therapeutic score (95-100% clearance) than those receiving UVB alone. In a recent RCT acitretin and UVB cleared 55.6% of patients compared with 63.3% treated with acitretin and PUVA.[22]

Acitretin and calcipotriol ointment
RCTs combining acitretin with calcipotriol ointment showed additive benefits of the combination with 67% patients showing clearance as compared with 41% with acitretin alone. In another study comparing the combination with acitretin monotherapy, the number of patients with complete clearance increased from 15% to 40% after 12 weeks[23] ($P < 0.05$). After 52 weeks, 60% and 40% in the combination and acitretin monotherapy group, respectively, achieved complete clearance. The duration of treatment and total dose of retinoids required to achieve clearance were slightly lower in the combination group, however, this was not statistically significant.

Other combinations
A RCT showed similar efficacy from the combination regimen of acitretin 0.4 mg/kg daily and etanercept 25 mg once weekly to that observed with etanercept 25 mg twice weekly thus proving etanercept-sparing effect of acitretin.[24]

The combination of methotrexate and acitretin has been used in patients with severe psoriasis, where all other treatments have failed. Although this combination can be very effective, sporadic severe hepatotoxic responses have been reported.[25]

The efficacy of concomitant use of acitretin with ciclosporin is not convincing as this combination can lead to ciclosporin toxicity as both drugs are inactivated by the same cytochrome P-450 system.[26]

In a randomized double-blind placebo controlled trial by Mittal et al., on 41 patients with psoriasis, 19 patients received combination of acitretin and pioglitazone while 22 received placebo with acitretin. After 12 weeks of therapy percentage reduction in PASI score was 64.2% in the acitretin plus pioglitazone group and 51.7% in the acitretin plus placebo group with minimal adverse events in both the groups. Thus, pioglitazone may have potential antipsoriatic effect and provide a convenient, efficacious, and relatively safe option to combine with acitretin.

OTHER USES

Darier’s disease
The results of multiple trials studying efficacy of acitretin and comparing with etretinate in Darier’s disease have shown marked improvement or remission in most of the cases even at low doses[27] (10-25 mg) and no significant difference in either of the two drugs.[28]

Pityriasis rubra pilaris
Isotretinoin is a first line therapy for pityriasis rubra pilaris, however, not so successful results have been reported for acitretin. There are individual case reports of success of acitretin therapy with UVB and UVA1 therapy in Pityriasis rubra pilaris (PRP) patients.[29]

Lichen planus
In a RCT in severe lichen planus, Laurberg et al., showed marked improvement in 64% of patients on acitretin 30 mg daily vs. 13% on placebo.[30] In a meta-analysis by Cribier et al., which included six studies with 86 patients with oral LP treated with etretinate, significant improvement occurred with etretinate over placebo.[31] Thus acitretin is favored as first-line therapy in cutaneous lichen planus. Acitretin may also be preferred in the hyperkeratotic variant of lichen planus for its modulating effect on keratinization. Jaime et al., reported a case of exuberant hypertrophic lichen planus involving palms and soles.
responding to acitretin with excellent response after 9 months of therapy.[32]

**Lupus erythematosus**

In an RCT of 58 patients comparing acitretin 50 mg daily with hydroxychloroquine 400 mg daily for 8 weeks, improvement was found in 46% and 50%, respectively, but drop outs were more frequent in the acitretin group because of side-effects.[33] In another open trial, 15 out of 20 subjects achieved total clearance or marked reduction in all lesions. Acitretin was found to be superior to previous therapy with antimalarials and/or systemic corticosteroids in most of the patients with subacute cutaneous lupus erythematosus who showed complete clearing of their lesions within 2-4 weeks.[34] Even in verrucous lesions of lupus it may have an edge over other agents as it modulates hyperkeratosis.

**Lichen sclerosus**

In a randomized controlled trial on 46 subjects, 14 of 22 patients on acitretin responded as compared to 6 of 24 in the placebo group. However, there was a high dropout rate in this study.[35]

**Ichthyosis and keratodermas**

Acitretin has been found to be useful in severe forms of the ichthyoses based on numerous clinical trials both in pediatric[36] and adult population.[37] These include lamellar ichthyosis, X linked ichthyosis, bullous, and nonbullous ichthyosiform erythroderma and Sjogren–Larsson syndrome. In these trials most patients have showed marked improvement or remission while on therapy.[38] Among the palmoplantar keratodermas, Vohwinkel syndrome, keratitis–ichthyosis–deafness (KID) syndrome, hereditary punctate palmoplantar keratoderma, type I hereditary punctate keratoderma, epidermolytic hyperkeratosis, and Papillon–Lefèvre syndrome have all been reported as successfully treated with acitretin in small series.[39-41] However, treatment of epidermolytic palmoplantar keratoderma may result in large erosions and worsening may occur in Netherton syndrome.[37] Acitretin has been reported to cause 51% reduction in hyperkeratotic hand eczema in one RCT of 29 patients.[42]

**Other conditions**

These are some of the off label indications of acitretin [Table 1].

**Infections**

Acitretin has also been found useful in the management of recalcitrant warts in numerous case reports,[43] especially involving difficult to treat sites, for example, scalp and periungual areas.[44] An open study of etretinate in children with severe warts showed clearance in 16 of 20 patients, however, in 4 patients there was relapse on stopping therapy.[45] Acitretin has been used as an adjunct to imiquimod therapy and excision in giant condyloma acuminata.[46]

In another case report acitretin improved clinical lesions of blastomycosis like pyoderma resistant to all conventional therapies within 3 months of starting treatment and there was nonrecurrence until 9 months of stopping therapy.[47] Acitretin has been reported to cause improvement with almost complete clearing in cutaneous lesions of a 64-year-old case of elephantiasis nostras verrucosa (nonfilarial in origin) with coexisting erythrodermic psoriasis.

Acitretin may also be proposed as a management option for morphea, post irradiation, as suggested in a case report of a 43-year-old patient of morphea treated with low dose acitretin and UV therapy.[48] There was subjective improvement in pain as well as objective improvement in degree of induration. It may also be useful in immunobullous disorders, for example,
subcorneal pustular dermatosis (SCPD) type of IgA pemphigus. In a case report of a patient with SCPD type of IgA pemphigus resistant to all modalities acitretin along with dapsone was found to cause clinical improvement.[49] A recent case report of a 57-year-old patient of Langerhans cell histiocytosis treated with one year of acitretin showed complete clearance of cutaneous lesions even at one year of follow-up. Presumably the action is attributed to the immunomodulator properties of acitretin on Langerhan cells.[50]

In a questionnaire-based retrospective cross-sectional survey by Gruber et al. conducted on 30 patients of Pachyonychia congenita the efficacy and side effects of oral retinoids (10-50 mg/day for 1-240 months) were assessed.[51] Overall, 30 patients were treated of which 12 patients received acitretin and 14 received isotretinoin. The therapy was effective in 58% and satisfaction score of 3.5 was achieved in acitretin group versus 36% and 2.1 for the isotretinoin group. There was significant improvement in hyperkeratosis in 50% of patients (P < 0.001). Overall, 14% patients had amelioration of their pachyonychia; while majority (79%) did not experience any nail change. All patients experienced adverse effects, and 83% discontinued medication. Risk/benefit analysis favored lower retinoid doses (≤25 mg/day) over a longer time period (>5 months), compared with higher doses (>25 mg/day) for a shorter time (≤5 months). Thus oral retinoids especially acitretin in lower doses may be considered a therapeutic modality in the management of pachyonychia congenita.

In a retrospective study of 12 patients with severe, recalcitrant Hidradenitis suppurativa, treated with acitretin for 9-12 months all patients achieved remission and significant improvement in pain, number of nodules and abscesses and long lasting improvement was noticed in 9 patients.[52] Thus acitretin may be used for its antiinflammatory properties in hidradenitis suppurativa. It also targets the process of hyperkeratosis of the infundibular follicular epithelium and eliminates the follicular mass of the keratinocyte–keratin complex.[52]

Acitretin has been reported to cause improvement in individual case reports in patients of porokeratosis with graft versus host disease, generalized linear porokeratosis, erosive pustular dermatosis of scalp, and lichen amyloidosis.[53-55]

**Prophylactic use (chemoprevention) or treatment of precancerous and malignant conditions**

There are case reports of acitretin used for prevention of cutaneous malignancies in solar-damaged skin and in genetic syndromes predisposing to skin cancer, for example, epidermodysplasia verruciformis,[56] graft versus host disease,[57] xeroderma pigmentosa,[58] keratoacanthoma,[59] basal cell naevus syndrome (etretinate). In epidermodysplasia verruciformis acitretin has been used as an adjunct in combination with interferon alfa-2a but as monotherapy was ineffective.[56] Acitretin has been reported as drug of choice in the management of keratoacanthomas and squamous cell carcinomas, giant basal cell carcinomas (as adjuvant therapy to surgical removal) in individual case reports.[59-61]

In a retrospective trial of 32 patients of cutaneous T cell lymphoma (CTCL) treated with acitretin of which 6 patients received monotherapy the overall response rate was 59% with mean duration of response being 28 months. Adverse effects were mild with discontinuation of therapy by five patients. Acitretin is well tolerated and potentially effective for early-stage CTCL. Thus response to acitretin, either as adjuvant therapy monotherapy, is comparable with the response to oral agents currently approved for CTCL.[62]

Chemoprevention with systemic retinoids has shown promising prospects in decreasing the incidence of new primary nonmelanoma skin cancers (NMSCs) in immunocompromised posttransplantation recipients. A review of three RCTs by Chen et al., showed significant decrease in the incidence of squamous cell carcinoma (up to 42%), basal cell carcinoma and premalignant lesions (actinic keratosis) in acitrein (not dose dependant) group compared with placebo over a follow up of 6-12 months.[63] However, a randomized controlled trial to assess the efficacy of acitretin as a chemopreventive agent in nontransplantation patients at high-risk for NMSC showed that there although there was a trend that favored the use of acitretin (P = 0.047) to prevent the incidence of NMSC and decrease the number of lesions, this was not a statistically significant benefit, possibly due to low statistical power.[64] Side-effects at higher doses lead to significant drop-outs. Overall, these were small studies with a modest reduction in cancer over a short period of observation, and further studies are required.
**CONTRAINDICATIONS**

The contraindications of acitretin have been enumerated in Table 2.

**Absolute**

The most important contraindication is female patients who are pregnant (CATEGORY X) or want to become pregnant in near future.

**Relative**

a. Neonates: Contraindicated in neonates unless the condition is life threatening (harlequin fetus)
b. Children: Should be monitored for bony side effects
c. Elderly: Higher risk of adverse events because of preexisting systemic or metabolic derangements
d. Patients with systemic diseases (hepatic/renal) or lipid derangements.

**Dosage**

Response to acitretin is dose dependent, with higher doses yielding greater and rapid improvement. However, adverse effects are also dose dependent, preventing use of higher doses of acitretin. The initial daily dose is 25 or 30 mg for 2-4 weeks, thereafter gradual dose escalation has been shown to be the most effective approach allowing gradual onset of 'tolerance' to side-effects.\[65\] Response is gradual peaking at 3-6 months with optimal dose in most patients being 25-50 mg/day up to a maximum of 75-100 mg. As relapse may occur within 2-6 months after discontinuing acitretin, so maintenance therapy is required in most patients based on clinical efficacy and tolerability, recommended dose being 20-50 mg daily which may be reduced to as low as 10-25 mg daily or 25 mg alternate day. It is available in 10 and 25 mg capsules and should ideally be taken with a fatty meal to enhance absorption.

Due to the uncertain effects of long-term acitretin therapy on growth and skeletal development, acitretin should only be used in pediatric patients with the most severe forms of keratinization disorders for which there are no effective alternative therapies.

In individual case reports in neonates and children acitretin given for congenital ichthyosis and harlequin ichthyosis was found to be safe and effective. It is given at a starting dose of 1 mg/kg body weight and thereafter daily doses can be titrated according to the clinical severity. In children on long-term therapy growth charting and annual screening radiography is advisable. It is advisable to freeze the capsule, cut it into a fraction depending on the dosage when giving to children. This can then be dispensed in children in a liquid like other solid tablets, which are crushed. The excessive part should be discarded as it is sensitive to light.

**Newer topical preparation**

Acitretin Nanostructured Lipid Carriers are prepared by solvent diffusion technique using 3 (2) full factorial design and NLCs incorporated in 1% w/w Carbopol 934 gel base. They are lyophilized and crystallinity of NLC characterized by Differential Scanning Calorimetry (DSC) and powder X-Ray Diffraction (XRD). *In vitro* skin deposition studies in Human Cadaver Skin and double-blind clinical studies in psoriatic patients were evaluated by Agrawal *et al.* to assess acitretin loaded Nanostructured Lipid Carriers (ActNLCs) and clinically evaluate the role of this gel in the topical treatment of psoriasis.\[66\] The optimized ActNLCs were spherical in shape, with average particle size of 223 (±8.92) nm, zeta potential of -26.4 (±0.86) mV and EE of 63.0 (±1.54). Significantly higher deposition of Acitretin was found in human cadaver skin from ActNLC gel (81.38 ± 1.23%) versus Acitretin plain gel (47.28 ± 1.02%). Clinical studies demonstrated significant improvement in therapeutic response and reduction in local side effects with ActNLCs loaded gel.

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**Table 2: Contraindications of acitretin therapy**

<table>
<thead>
<tr>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Lactating mothers</td>
</tr>
<tr>
<td>Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years</td>
</tr>
<tr>
<td>Except under special circumstances, acitretin should not be used when the following medical problems exist</td>
</tr>
<tr>
<td>Allergy to parabens</td>
</tr>
<tr>
<td>Hyperlipidemia, intractable (especially those with diabetes mellitus, obesity, increased alcohol intake, or familial history), or</td>
</tr>
<tr>
<td>Pancreatitis or history of Hypervitaminosis A, or history of or</td>
</tr>
<tr>
<td>Hypersensitivity to etretinate, isotretinoin, tretinoin, or vitamin A</td>
</tr>
<tr>
<td>Risk-benefit should be considered when the following medical problems exist</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1 or 2 or</td>
</tr>
<tr>
<td>Hepatic disease,</td>
</tr>
<tr>
<td>Renal disease</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Concomitant intake of hepatotoxic drugs</td>
</tr>
<tr>
<td>Concomitant intake of drugs which interfere with its metabolism</td>
</tr>
</tbody>
</table>

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thus offering a ray of hope for the future management of psoriasis using topical formulation of acitretin.

**Monitoring**

Liver enzymes, fasting serum cholesterol and triglycerides and blood sugar (in diabetics) every 2-4 weeks for the first 2 months of therapy and then every 3 months. If liver function tests are abnormal, weekly checkups should be done and acitretin dose adjusted accordingly. Acitretin should be discontinued if transaminases are elevated to three times their upper normal limit, and patients with bilirubin >50 μmol/L (3 mg/dL) or alanine aminotransferase >200 IU/L should be referred to gastroenterology. If the levels are between 2 and 3 times the normal range, acitretin should be discontinued till they become normal and then restarted at lower doses. If they are elevated only two times then the levels usually resolve even on therapy. However, frequent monitoring is required. Similarly, patients with triglycerides >5 mmol/L (442.48 mg/dL) should be referred to a lipidologist and hypertriglyceridaemia more than 10 mmol/L (884.96 mg/dL) warrants discontinuation of acitretin.

**Side effects**

All side effects that have been reported for acitretin in the literature are dose-dependent and reversible, except for hyperostosis [Table 3].

**Teratogenicity**

There have been a lot of case reports of fetal malformations associated with acitretin use during pregnancy leading to retinoid embryopathy. Retinoid embryopathy can result in craniofacial dysmorphias such as high palate and anophthalmia, abnormalities of appendages including syndactyly and absence of terminal phalanges, malformations of the hip, meningoencephalocele, and multiple synostosis. Acitretin is teratogenic regardless of the duration of treatment or dosage used especially in the first trimester. Two forms of effective contraceptives should be used, beginning one month prior to starting Acitretin, throughout the duration of treatment and for 2 years in Europe and 3 years in US after stopping. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: Tubal ligation, partner’s vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include latex condoms (with or without spermicide), diaphragms, and cervical caps (which must be used with a spermicide). Acitretin interferes with the action of microdosed progestin (‘minipill’) oral contraceptives. So it is not advisable to use this type of birth control while taking acitretin. In women

### Table 3: Side/adverse effects of acitretin

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teratogenicity</strong></td>
<td></td>
</tr>
<tr>
<td>Those indicating need for medical attention</td>
<td></td>
</tr>
<tr>
<td>Incidence more frequent</td>
<td>Arthralgia, Hypertonia, Myalgia, Spinal hyperostosis, Headache, Nausea, Vomiting</td>
</tr>
<tr>
<td>Incidence less frequent</td>
<td>Ophthalmologic effects, including blepharitis, conjunctivitis, eye irritation, photophobia or other visual problems (blurred vision; eye pain; loss of eyelashes; redness or swelling of the eyelid; redness of the eyes; sensitivity of eyes to light; watery eyes), cortical, nuclear, and posterior subcapsular cataracts, pannus, or subepithelial corneal lesions, decreased night vision, pseudotumor cerebri or recurring sty or paronychia</td>
</tr>
<tr>
<td>Incidence rare</td>
<td>Dermatologic effects, such as abnormal skin odor, dermatitis or psoriasiform rash, fissuring, hypertrophy, infection or ulceration of skin, pyogenic granuloma, purpura, otitis externa, paresthesia</td>
</tr>
<tr>
<td>Systemic side effects</td>
<td>Hepatitis, Hyperlipidemia, Pancreatitis, Influenza-like symptoms, Laryngitis or pharyngitis</td>
</tr>
<tr>
<td>Those indicating need for medical attention only if they continue or are bothersome</td>
<td></td>
</tr>
<tr>
<td>Incidence more frequent</td>
<td>Alopecia, Mucocutaneous: Chapped lips or cheilitis, ceruminosis, dry, irritated mucous membranes of nose or rhinitis, pruritus, scaling and peeling of eyelids, fingertips, palms, or soles of feet and sticky skin, Difficulty in wearing contact lenses, Gingivitis or stomatitis, Photosensitivity, Xerophthalmia, Unusual thirst</td>
</tr>
<tr>
<td>Incidence less frequent</td>
<td>Constipation, Diarrhea, Fatigue, Increased sweating, Vulvovaginitis</td>
</tr>
</tbody>
</table>


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of childbearing age, pregnancy must be excluded by two negative pregnancy tests with a sensitivity of at least 25 mIU/mL with second test to be done during the first 5 days of the menstrual period immediately preceding the beginning of acitretin therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse and acitretin should be started only on the second or third day of the next menstrual cycle. Regular tests (ideally every month) should be done to rule out pregnancy. The patients of childbearing age should be advised to abstain from alcohol during and 2 months after the cessation of therapy as alcohol intake increases the metabolism of acitretin to etretinate. However, risks from semen of men taking acitretin have not been reported. Blood transfusion is, however, contraindicated for all patients on acitretin therapy.

**Mucocutaneous**
Mucosal involvement may lead to epistaxis and rhinitis, and ocular disturbances including photophobia, xerophthalmia, and conjunctivitis. Cheilitis, dry mouth, stomatitis, gingivitis, and taste disturbances have been reported. Thinning, redness, and scaling may occur, particularly on the palms and soles. Increased hair loss (up to 75% patients), nail fragility, paronychia and periungual pyogenic granuloma may occur. Rarely, patients may experience photosensitivity reactions and ‘retinoid dermatitis’, which resembles unstable psoriasis can also develop in up to 25% of patients receiving high-dose oral acitretin. In a retrospective analysis of 176 patients receiving acitretin, cheilitis occurred in approximately 60-75% patients, skin peeling in 25-50%, rhinitis in 20-30%, dry skin in 15-25%, and hair loss in 10-25%. Other effects such as sticky skin, rigors, itchiness, and dry mouth were less common, occurring in fewer than 25% of patients, even in those receiving the highest doses. These mucocutaneous side effects can be treated symptomatically and do not require discontinuation of therapy. Although most of the studies suggest these side effects to be dose related, there are studies that refute it.

**Hepatotoxicity**
Use of acitretin may cause transient and reversible elevation in serum liver enzymes in up to 15% of patients. However, severe hepatotoxic reactions (severe cholestatic hepatitis/cirrhosis) and overt hepatitis are rare (0.26%). Frequent monitoring of liver function is recommended in alcoholics, diabetics, obese individuals, and patients with concurrent use of other hepatotoxic agents.

**Hyperlipidemia**
Retinoid therapy may cause changes in the serum lipid profile especially increase in triglycerides and cholesterol and decrease in high density lipoprotein (HDL). The greatest increase is seen in triglycerides, which occurs in 20-40% of patients while hypercholesterolaemia, is seen in 10-30% of patients due to increases in both the VLDL and/or low density lipoprotein (LDL) fractions and decrease in the HDL fraction (40% patients) leading to increased risk of developing cardiovascular disease. One case of fatal fulminant pancreatitis due to hypertriglyceridemia has been reported. These effects are reversible and can be managed by dietary modifications, fish oil rich diet, oral hypolipidemic drugs or decreasing acitretin dose. In a retrospective analysis on side effect profile of 525 patients receiving acitretin therapy in doses 10-75 mg/day, increased triglyceride levels occurred in 66% and total cholesterol increased in 33% of patients.

**Pancreatitis**
Increase in serum triglycerides levels leading to pancreatitis is uncommonly reported (single case). However, patients with diabetes mellitus, obesity, increased alcohol intake, or a family history of hypertriglyceridemia have increased predisposition to this complication.

Pseudotumor cerebri or benign intracranial hypertension has been reported rarely with acitretin especially in patients with concurrent tetracycline or minocycline administration leading to headache, visual changes, nausea, or vomiting and papilledema. Such patients should discontinue acitretin immediately and shall be referred for neurological evaluation.

**Hyperostosis**
Long-term (2-4 years) treatment with acitretin has been associated with radiographic evidence of extraspinal tendon and ligament calcification, the most common sites being ankles, pelvis, and knees. Diffuse idiopathic skeletal hyperostosis (DISH)-like involvement, characterized by degenerative spondylosis, vertebral arthritis, and syndesmophytes of the vertebral spine, has also been reported but these changes have found no correlation with dose or duration of treatment. Occasional reports of bone changes including premature epiphyseal closure, skeletal hyperostosis, and extraosseous calcification
have been reported in pediatric age group. However, recent studies do not focus on any growth or bony abnormalities in patients on long-term retinoids.[73] Thus routine annual radiography is not warranted in adults unless symptomatic. Pretreatment X-rays for bone age including X-rays of the knees or ankles are generally advised in children. Bone scans (scintigraphs) and/or X-rays should be considered at yearly intervals when monitoring children on long-term therapy. Atypical musculoskeletal pain or limitation of movement should be evaluated by appropriate radiological examination. 

Recent British Association of Dermatology (BAD) guidelines, however, do not recommend routine radiography for monitoring in children unless warranted as it may cause unnecessary radiation exposure. However, growth charting should be done for children on acitretin to detect premature closure at early stage. Other rheumatological manifestations that may occur during therapy with acitretin include arthralgias, arthritis, myalgias, osteopenia and a few cases of vasculitis, Wegener granulomatosis, and erythema nodosum.[13]

Other side effects
Vulvovaginitis, increased insulin sensitivity, and delayed wound healing have also been reported.[13] Acitretin although leads to excessive granulation tissue formation, does not significantly affect wound healing. In a study of 44 complex wounds in transplant recipients by Tan et al., there were no significant effects on wound infection, dehiscence, hypertrophic scarring, or hypergranulation. There is therefore no need to stop acitretin for routine surgery such as orthopedic procedures.

DRUG INTERACTIONS

Tetracycline and minocycline: Increased photosensitivity, pseudotumor cerebri (although the single case report of pseudotumor reported with acitretin was not associated with tetracycline intake)

Alcohol
Increased conversion to etretinate, hepatotoxicity.

Vitamin A supplements
Hypervitaminosis. Intake should not exceed the recommended dietary allowance (2400-3000 IU daily).

Antidiabetic agents
Alterations in blood glucose may occur. In a study of seven healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide in three of the seven subjects. Repeating the study with six healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with acitretin is therefore recommended.

Corticosteroids
Hyperlipidemia, pseudotumor cerebri.

Methotrexate and other hepatotoxic drugs
Increased methotrexate level, hepatotoxicity.

Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-cis form (cis-acitretin) in the liver by cytochrome enzymes. The concomitant administration of methotrexate or other hepatotoxic drugs that are also metabolized in liver by these enzymes thus alters the pharmacodynamics with increased blood levels of methotrexate and further hepatotoxicity.

Progestosterone pills (“minipill”) preparations
Acitretin decreases the antiovulatory effect of the progestin only pill (mini-pill) but has no effect on the combined preparations.

Excessive exposure to sunlight or phototoxic drugs: Increased photosensitivity.

Thus, Acitretin monotherapy is recommended in the treatment of:[13]

1. Severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments (A, 1+)
   1a. In combination with PUVA therapy or narrowband phototherapy (A, 1+)
   1b. In combination with calcipotriol ointment (A, 1+)
2. Palmoplantar pustular psoriasis (A, 1+)
3. Hyperkeratotic hand eczema (A, 1+)
4. Severe Darier disease (A, 1+)
5. Severe congenital ichthyosis (D, 3)
6. Keratoderma (D, 3).
7. Lichen planus (A, 1+)
8. Lichen sclerosus (A, 1+)
9. Discoid lupus erythematosus (A, 1+)
CONCLUSION

Acitretin has been found to be effective in psoriasis, keratinization disorders, inflammatory dermatosis, and as an antineoplastic agent. Despite being associated with a wide range of side effects, the benefits of its use scores over the side effects. However, teratogenicity is a serious concern and adequate monitoring is required especially in higher risk groups.

REFERENCES


Multiple choice questions

1. All of these are first generation retinoids except:
   a. Tretinoin
   b. Isotretinoin
   c. Alitretinoin
   d. Acitretin

2. The following are actions of acitretin useful in psoriasis except:
   a. Regulating increased proliferation rate
   b. Normalizing epidermopoesis
   c. Antiinflammatory
   d. Antineoplastic

3. Acitretin has synergistic action with all of the following agents in treatment of psoriasis except:
   a. Coal Tar
   b. Topical Steroids
   c. PUVA
   d. UVB

4. Acitretin has been reported useful in all of the following precancerous/cancerous conditions except:
   a. Epidermodysplasia verruciformis
   b. Arsenical keratosis
   c. Keratoacanthoma
   d. Malignant melanoma

5. All the side effects of acitretin are dose dependent except:
   a. Hypertriglyceridemia
   b. Hyperostosis
   c. Elevated liver enzymes
   d. Mucocutaneous

6. The following is not a reported side effect of acitretin:
   a. Chelitis
   b. Hypertrichosis
   c. Pyogenic granuloma
   d. Conjunctivitis

7. Acitretin has been reported to cause the following metabolic derangements except:
   a. Hypertriglyceridemia
   b. Hypercholesterolemia
   c. Elevated liver enzymes
   d. Elevated levels of phenyl alanine

8. Acitretin may cause drug interactions with the following group of drugs:
   a. Penicillin group of antibiotics
   b. Antihypertensives
   c. Progesterone pills
   d. Antiinflammatory agents

9. The following indication warrants discontinuation of acitretin:
   a. Liver enzymes raised twice the normal levels
   b. Blood cholesterol levels raised by 10%
   c. Liver enzymes raised more than three times the normal value
   d. Photosensitivity

10. Acitretin finds its use in the following group of ichthyosis disorders except:
    a. Lamellar ichthyosis,
    b. X linked ichthyosis
    c. Sjogren–Larsson syndrome
    d. Netherton syndrome

Answers:
1. d,  2. d,  3. a,  4. d,  5. b,  6. b,  7. d,  8. c,  9. c,  10. d
Estimation of serum level of interleukin-17 and interleukin-4 in leprosy, towards more understanding of leprosy immunopathogenesis

Marwa Abdallah, Hanaa Emam, Enas Attia, Jihan Hussein, Noha Mohamed

ABSTRACT

Background: Combating Mycobacterium leprae is known to be via T-helper1 response. However, other T-helper effector cells; T-helper17 and T-helper2; play a role, particularly in the context of disease type. Aims: We aimed to evaluate serum levels of interleukin (IL)-17 (T-helper17 cytokine) and IL-4 (T-helper2 cytokine) in untreated patients with different types of leprosy, compared to controls. Methods: Using enzyme-linked immunosorbent assay, serum IL-17 and IL-4 levels were estimated in 43 leprotic patients and 43 controls. Patients were divided into six groups; tuberculoid, borderline cases, lepromatous, erythema nodosum leprosum (ENL), type 1 reactional leprosy, and pure neural leprosy. Patients were also categorized according to bacillary load and the presence or absence of reactions. Results: Serum IL-17 was significantly lower in cases (4-61.5 pg/mL; median 19), compared to controls (26-55 pg/mL; median 36) (P < 0.001), and was significantly lower in each type of leprosy compared to controls, with the lowest level in lepromatous leprosy (4-61.5 pg/mL; median 12.5). Significantly elevated serum IL-4 was found in patients (1.31-122.4 pg/mL; median 2.31) compared to controls (1.45-5.72 pg/mL; median 2.02) (P = 0.008), with the highest level among lepromatous leprosy patients (2-87.2 pg/mL; median 28.9), and the lowest in type 1 reactional leprosy (1.4-2.5 pg/mL; median 1.87) (P = 0.006). Conclusion: Defective secretion of IL-17 is related to disease acquisition as well as progression toward lepromatous pole in leprosy patients. The overproduction of IL-4 in patients with lepromatous leprosy may infer their liability to develop ENL. Nevertheless, the small number of the studied population is a limitation.

Key words: Interleukin-4, interleukin-17, leprosy

INTRODUCTION

Leprosy is a chronic granulomatous infection caused by the obligate intracellular organism; Mycobacterium leprae (M. leprae). According to Ridley and Jopling, leprosy is classified into tuberculoid (TT), borderline tuberculoid (BT), midborderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL). At one pole, TT leprosy is characterized by few bacilli (paucibacillary; PB) and vigorous cell-mediated immunity (CMI). At the other pole, lies LL, with numerous bacilli (multibacillary; MB), and inefficient CMI. TT is characterized by a predominance of CD4+ T cells and type-1 cytokines. In contrast, LL is characterized by predominance of CD8+ T cells and type 2 cytokines. Between those two polar forms, lie the borderline forms, liable to reactional leprosy (RL) type 1, with a predominantly type-1 cytokine profile. Erythema nodosum leprosum (ENL), which manifests in BL and LL
leprosy patients, is a more systemic reaction than the previous.\textsuperscript{[11,12]} The aforementioned data demonstrate the immunopathological interactions between type 1 and type 2 cytokines\textsuperscript{[13,14]} and activated macrophage products (monokines) in leprosy.\textsuperscript{[15]} However, certain T cell subset were shown to produce cytokines that could not be classified according to the Th1-Th2 scheme.\textsuperscript{[13,14]} Interleukin (IL)-17 was among these cytokines\textsuperscript{[16]} and T cells producing IL-17 were named Th17 cells.\textsuperscript{[17,18]} Thus, we aimed in this study to evaluate serum levels of IL-17 and IL-4 in untreated leprosy patients, compared to healthy controls, to gain further insight into the role of these cytokines in the immunopathogenesis of leprosy.

METHODS

This study was conducted on 43 untreated leprotic patients attending at El Qal’aa Dermatology and Leprosy Hospital, Cairo, Egypt, and 43 healthy volunteers as a control group, after signing an informed consent, over a period of 10 months. The study was conducted according to the Declaration of Helsinki and was approved by the medical ethical committee of Ain Shams University, as well as National Research Institute. Patients were evaluated according to clinical examination, slit skin smear examination (SSS), and histopathological examination, and were divided into six groups: Group A: LL; Group B: TT; Group C: Borderline leprosy (BT, BB, and BL); Group D: RL type 1, Group E: ENL; and Group F: Pure neural leprosy (PNL). The patients were also categorized according to the presence or absence of RL into non-RL, including Groups A, B, C, and E, and RL, including Group D patients. In addition, 43 healthy age- and gender-matched subjects, with negative hepatitis C virus and hepatitis B virus serology and negative tuberculin test, were also included in the study, comprising the control group.

Blood samples were collected from both patients and controls, provided that all subjects were free of any other systemic disease. We excluded patients who started antileprotic treatment or who were taking any kind of immunomodulatory therapy likely to alter the results of the study, such as systemic corticosteroids. Blood was collected in sterile test tubes and centrifuged for 15 min at 50 g. Serum was separated and kept at −70°C until used for estimation of IL-4 and IL-17 by enzyme-linked immunosorbent assay (ELISA). IL-4 was quantitatively estimated by the RayBio® human ELISA kit (RayBio®, IL4-001, 2010, USA) according to the method described by Paul and Ohara (1987).\textsuperscript{[19]} IL-17 was estimated by the RayBio® human ELISA kit (RayBio®, IL17-001, 2010, USA) according to the method described by Numasaki et al.\textsuperscript{[20]}

Statistical analysis was done using SPSS (statistical program for social science) version 12. Mann-Whitney test for pair wise comparisons. Kruskal-Wallis test with Bonferroni adjustment was used for multiple comparisons. Spearman correlation was used to measure the correlation between the quantitative variables. A “$P$” < 0.05 was considered significant, while <0.001 was highly significant.

RESULTS

The current study included 43 leprotic patients; 16 females (37.2%) and 27 males (62.8%). Their ages ranged from 15 to 65 years (mean ± standard deviation (SD) = 35.74 ± 11.23). Forty-three apparently healthy individuals served as controls; 16 females (37.2%) and 27 males (62.8%). Their age ranged from 15 to 60 years (mean ± SD = 36 ± 13.703). SSS was negative in 16 patients (37.2%), grouped as PB, while it was positive in 27 patients (62.8%); grouped as MB.\textsuperscript{[21]} The patients subgroups were: Group A: 11 patients (25.6%) with LL, Group B: 6 patients (14%) with TT, Group C: 9 patients (20.9%) suffering from borderline leprosy (5 with BT, 3 with BB, and 1 with BL), Group D: 6 patients (14%) suffering from RL type 1, Group E: 6 patients with ENL (14%), and Group F: 5 patients (14%) suffering from PNL. Non-RL category included 31 patients (72.1%) from Groups A, B, C, and F, while RL included 12 patients (27.9%) comprising of group D and E patients.

Leprosy patients showed significantly lower IL-17 level (4-61.5 pg/mL; median of 19), compared to controls (26-55 pg/mL; median of 36) ($P < 0.001$). On comparing serum IL-17 level in patients with negative versus positive SSS, it ranged from 12.5 to 49 pg/mL (median = 20) in PB cases compared with 4-61.5 pg/mL (median = 19) in MB patients ($P = 0.989$). IL-17 was highest among TT (range: 14-49 pg/mL; median 21). The lowest level was detected in LL type (range: 4-61.5 pg/mL; median 12.5), with no statistically significant difference ($P = 0.223$). Nevertheless, statistically significant difference was found on comparing serum IL-17 levels in different types of leprosy with controls (median of 12.5 pg/mL in LL,
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21 pg/mL in TT, 19 pg/mL in borderline, 19.5 pg/mL in RL Type 1, 20 pg/mL in ENL, and 14 pg/mL in PNL; compared to 36 pg/mL in controls) ($P = 0.007, P = 0.005, P = 0.018, P = 0.005, P < 0.001, and P < 0.001$, respectively). Yet, serum IL-17 levels were not statistically different in non-RL compared with RL patients (range: 4-61.5 pg/mL and median 17 vs. range: 12.5-50 and median 20, respectively) ($P = 0.671$).

Regarding serum IL-4, comparing patients and controls revealed highly significantly elevated serum IL-4 in patients compared to controls (range: 1.31-122.4 pg/mL and median 2.31 vs. range: 1.45-5.72 pg/mL and median 2.02, respectively) ($P = 0.008$). According to SSS, the level of IL-4 ranged from 1.87 to 7.26 pg/mL with a median of 2.24 in PB cases, while it ranged from 1.31 to 22.40 pg/mL with a median of 2.42 in MB cases ($P = 0.773$). IL-4 was highest among LL patients, ranging from 2 to 87.2 pg/mL (median = 28.9). The lowest level detected was in RL type 1, ranging from 1.4 to 2.5 pg/mL (median = 1.87). A statistically significant difference was found when comparing all groups (median of 28.9 pg/mL in LL, 2.67 pg/mL in TT, 1.94 pg/mL in borderline, 1.8 pg/mL in RL type 1, 2.4 pg/mL in ENL, and 2.1 pg/mL in PNL) ($P = 0.006$). Furthermore, serum level of IL-4 was statistically significantly higher in LL patients, compared to each of ENL, type 1 RL, borderline, and PNL groups ($P = 0.15, 0.002, 0.01$, and $0.009$, respectively). Compared to controls, IL-4 level was statistically significantly higher in LL patients and TT patients (median of 28.9 and 2.67 pg/mL, respectively vs. 2 pg/mL for controls) ($P < 0.001$ and $P = 0.04$, respectively). Yet, serum IL-4 levels were not statistically different when comparing non-RL with RL (range: 1.31-87.2 pg/mL and median 2.31 pg/mL vs. range 1.43-3.5 pg/mL and median 2.1) ($P = 0.068$).

Negative correlation was detected between serum levels of both IL-17 and IL-4, but the results were not statistically significant ($r = -0.171, P = 1$) [Figure 1].

**DISCUSSION**

Hereby, it is worth mentioning that, to the best of our knowledge, Th17 and its cytokine profile were not studied in leprosy before. Th17 mechanism of induction and their effector function is nowadays the focus of important studies in immunology.$^{[22]}$ IL-17 was significantly lower in our cases compared to controls (the lowest in LL while the highest in TT). Studies on infection models described significant role of IL-17 level in mycobacterial infections; namely *M. tuberculosis*.$^{[23]}$ Susceptibility to pulmonary *M. avium-intracellulare* complex may be associated with biases in Th1/Th2/Th17 immunity.$^{[24]}$ Moreover, Th17 cells can provide interferon (IFN)-$\gamma$-independent protection against *M. tuberculosis*.$^{[25]}$ In accordance, in patients with tuberculosis disease, IL-17 was not detected in bronchoalveolar lavage fluid, which may be due to suppression by Th1 cytokines, including IFN-$\gamma$.$^{[26]}$ Thus, Th1 and Th17 responses cross-regulate each other during mycobacterial infection.$^{[27]}$ Another infection with similar pathology is leishmaniasis. The weak type 1 immune response observed in *L. braziliensis* infection may be mediated by poor innate immune response with impaired IL-17.$^{[28]}$ Therefore, we speculate that such an inherent deficiency can also contribute to the development of leprosy and even to disease progression toward the MB pole.

The hypothesis that the spectrum of leprosy reflects the balance between Th1 and Th2 populations is indeed exciting.$^{[13]}$ In TT, there is good evidence of predominant IL-2 and IFN-$\gamma$ production, while LL patients have mainly cytokines of a Th2 type, including IL-4.$^{[10]}$ In accordance, we revealed significantly elevated IL-4 in patients, being highest among LL patients, and lowest in type 1 RL. Type 1 RL is associated with an overproduction of Th1-type cytokines.$^{[15]}$ Since Th1 and Th2 cells can cross-regulate one another; IFN-$\gamma$ directly suppresses IL-4 secretion and Th2 polarization,$^{[29]}$ which is evident in type 1 RL. On the contrary, type 2 reactions occur in patients with poor CMI to *M. leprae*, abundant bacilli, and a strong polyclonal antibody response. In addition, increased IL-8 and IL-10, and sustained expression of IL-4 and IL-5; all cytokines associated with neutrophil chemotaxis and antibody...
production were observed in ENL lesions. However, there is also evidence of enhanced production of TNF-α and IL-6, and increased circulating IL-2 receptors in acute ENL episodes causing nerve destruction. These findings can explain why serum IL-4 was not different in ENL patients compared to controls and other disease categories. On comparing serum IL-4 level in patients with PB versus MB leprosy, no significant difference was found. Moreover, no difference was detected, comparing RL to non-RL. In contrast, El Saadany et al. showed a significant difference in IL-4 among non-RL, type 1 reaction, and type 2 reaction, with a tendency to increased levels more in type 2 reaction. This data agrees with Verhagen et al. who stated that IL-4/IL-4 mRNA was produced predominantly from a BL patient. Since IL-4 inhibits CMI responses and favors humoral immunity, IL-4 might contribute to high antibody levels and unrestricted replication of bacilli in such patients. Studying this cytokine profile in both sera and tissues of larger leprosy population is recommended to clarify these points. Surprisingly, our TT patients had elevated IL-4 compared to controls. In contrast, Spellberg and Edwards explained the absence of mRNA for IL-4 in BT or BB lesions, by the presence of Th1 cytokines IL-12 and IFN-γ. This discrepancy can be due to the difference between lesional and circulating cytokine profile, particularly toward the tuberculoid pole, the well-known of localized neurocutaneous disease, rather than being systemic disease, for further investigations. Negative correlation was detected between serum levels of both IL-17 and IL-4, but with no statistical significance. Since IL-17 is related to protective mechanisms against disease progression, while IL-4 could be related to disease progression, with Th2 activation; further, studies on larger number of patients can obviate a significant negative correlation between them.

Limitation

- The small number of patients prevented us from drawing solid conclusions.
- The absence of repeated measurements in the same individuals to evaluate whether treatment can attenuate this immune dysregulation is another limitation.

CONCLUSION

It seems that defective secretion of IL-17 has a role in leprosy progression. Targeting Th17 or IL-17 can be a future helpful approach to limit this endemic disabling disease. Since, M. bovis BCG-specific Th17 cells confer partial protection against M. tuberculosis infection, the application of M. leprae-specific Th17 could be promising in the context of leprosy. On the contrary, the overproduction of IL-4 in MB leprosy patients may result in their liability to develop ENL. Approaches of IL-4 antagonism include soluble recombinant human IL-4 receptor; altrakincept and a variant form of IL-4; pitrakinra. To our knowledge, the use of such compounds in treatment of other IL-4-related disorders, such as BL and LL patients is not documented yet, for future trials.

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REFERENCES


Prevalence and risk factors of onychomycosis in primary school children living in rural and urban areas in Central Anatolia of Turkey

Mustafa Gulgun, Elcin Balci, Abdulbaki Karaoglu, Vural Kesik, Oguzhan Babacan, Muzaffer Kursat Fidanci, Turker Turker, Duran Tok, Nedret Koc

ABSTRACT

Background: Onychomycosis is a world-wide public health concern in children, requiring epidemiological data for different regions for control and prevention. Aim: The aim of this study was to evaluate the predominant pathogens and risk factors for onychomycosis in school children living in Kayseri, Turkey. Methods: This study included 8122 school children, aged 5-16 years, living in the rural and urban areas around Kayseri. Onychomycosis was clinically classified as distal and lateral subungual (DLSO), proximal subungual, superficial white, endonyx and totally dystrophic onychomycosis. Nail samples from children with clinically diagnosed onychomycosis were collected, examined by direct microscopy and inoculated for culture study. The demographic features and possible risk factors were recorded and assessed by logistic regression models. Results: We clinically diagnosed onychomycosis in 152 out of 8,122 (0.18%) school children. DLSO was the most frequent clinical diagnosis (120/152, 78.9%). Culture-positive onychomycosis was detected in 27/152 (17.7%) children. The prevalence of culture-positive onychomycosis was determined as 0.33%. All culture-positive samples were only from toenails. The onychomycosis causative agents were dermatophytes in 17/27 cases (62.9%), including Trichophyton rubrum (12, 44.4%), Trichophyton mentagrophytes 1 (3.7%), Trichophyton tonsurans 1 (3.7%) and Trichophyton spp. 3 (11.1%) and yeasts in 10/27 cases (37.1%), including Candida glabrata 4 (14.8%), Candida parapsilosis 1 (3.7%), Trichosporon 2 (7.4%) and Rhodotorula 3 (11.1%). Age, father’s occupation, number of siblings and rooms were statistically associated with the frequency of onychomycosis. Conclusions: Although the prevalence of onychomycosis in school children in central Anatolia of Turkey seems very low degree, pediatric onychomycosis is a growing public health concern all over the world. Children having more siblings or unemployed fathers and children living in small house as well as older children should be examined carefully for onychomycosis. Key words: Dermatophytes, epidemiology, pediatric onychomycosis, school children, yeasts

INTRODUCTION

Onychomycosis can be caused by dermatophytes, yeasts and non-dermatophyte molds that are transmitted through infected moist floor areas and less often transmitted via direct personal contact.[1] In Europe, North America and Turkey, the most common etiologic agents of onychomycosis are dermatophytes, in children and adults, whereas yeasts are the most common in Saudi Arabia and Pakistan in the general population.[2-5] Non-dermatophyte molds are accepted as uncommon or secondary pathogens in onychomycosis in already damaged nails by trauma, ischemia or disease, especially dermatophyte infection and frequently seen in elderly, immunosuppression, poor peripheral
circulation or temperate climates. The prevalence of onychomycosis is low among children compared with adults due to reduced exposure to infected environments (communal showers, public changing rooms and saprophytic fungi), faster linear nail growth, less cumulative trauma due to smaller and thinner nail surface and lower prevalence of tinea pedis.

Epidemiologic surveys depicted the prevalence of onychomycosis in children <16 years of age ranging from 0.2% to 2.6%. The prevalence of onychomycosis varies depending on age, sex, regional differences, cultural habits, migration, seasonal conditions, immune status of the host, living and hygienic conditions. It is therefore essential to obtain epidemiological data for different regions to enable strategic planning for control and prevention. No data are available on the prevalence and common etiologic agents of onychomycosis in children in our region.

The aim of this study was to estimate the prevalence of onychomycosis in school children living in rural and urban areas of central Anatolia of Turkey and to determine the risk factors for infection.

METHODS

This cross-sectional epidemiological study was conducted in school children in Kayseri, a city with a total of 139,422 school children in central Anatolia, Turkey. The climate in Kayseri is cold, snowy and wet in winter while dry and hot in summer. The lowest and highest temperature in Kayseri are −5.2°C and +25.7°C (mean 7.73°C). Mean humidity is 69.3%. This study was approved by the Erciyes University Ethics Committee. A total of 8,122 children, aged 5-16 years, from randomly selected 24 primary schools located in Kayseri were selected by cluster sampling method and examined for onychomycosis at the first visit. Clinical examination of fingernails and toenails was performed by a pediatrician and a medical physician specialized on public health at the same time. Inclusion criteria were school children aged 5-16 year-old studying in Kayseri. Exclusion criteria were <5 or >16 years old.

Onychomycosis was clinically classified as distal and lateral subungual (DLSO), proximal subungual (PSO), superficial white (SWO), endonyx and totally dystrophic (TDO) onychomycosis. If there was onycholysis and subungual hyperkeratosis, thickening or distortion of the nail plate, it was diagnosed as DLSO. It was considered as PSO in the evidence of subungual hyperkeratosis, transverse leukonychia, proximal onycholysis or destruction of the proximal nail plate. The diagnosis of SWO was defined as homogenously white nail, diffusely opaque with variable pigmentation, flexible and friable. Nails with diffuse milky-white discoloration, with normal thickness and normal plate surface, in the absence of nail bed hyperkeratosis or onycholysis were diagnosed as endonyx. If there was total destruction of the entire nail plate including whole thickness of the plate, the nail bed and matrix and if dystrophic and thick nail crumbled and disappeared leaving a thickened abnormal nail bed retaining keratotic nail debris, this clinical pattern was diagnosed as TDO. Paronychia was determined if there was painful swelling and erythema of the proximal and lateral nail folds. When onychomycosis was clinically diagnosed, samples from clinically suspected nails after cleaning with 70% alcohol were collected by scraping or shaving from the distal portion of the nail, the proximal nail bed, the undersurface of the nail plate, the friable area of leukonychia, hyperkeratotic nail bed, opaque white area and proximal, distal and lateral nail edge with a disposable scalpel or curette. Onycholytic nail plate was removed before sampling. Outermost debris was discarded. Child’s feet with abnormal onychomycosis-suspected areas were also examined for desquamation and/or scaling, plantar fissures, discoloration, and groove. When tinea pedis was suspected, samples from the feet skin, interdigital surfaces, toe web or the surrounding skin were collected. After samples were examined with 15% potassium hydroxide (KOH) solution by direct microscopy, the samples were cultured according to literature. Isolated yeast that did not form a germ tube was identified by the growth properties in corn-meal agar and by using ID 32 C (Bio-Merieux, Marcy l’Etoile and France). Dermatophytes when isolated were accepted as the causative agent and a patient of onychomycosis was diagnosed when a positive culture was detected for a dermatophyte.

C. albicans was regarded as the primary pathogen on repeated isolation along with a direct microscopy outcome demonstrating yeast pseudomycelia. Non-C. albicans spp. were admitted as the primary pathogen with two or more isolation as long as there was yeast pseudomycelia in direct microscopic examination and no other concomitant pathogen.
Candida spp. was taken into account as the secondary pathogen if they were isolated with dermatophyte or non-dermatophyte pathogenic mold with microscopy revealing budding yeast cells.

The following details were recorded for each child: Age, sex, school grade, number of siblings, parents’ educational and occupational status, family income, frequency of having baths (per week) and sock changing, animal husbandry, school settlement, number of rooms and types of shoes.

Statistical analysis was conducted using the package SPSS 15.0 (Chicago, IL). Categorical variables were defined as the number and percentage (%) and analyzed using the Chi-square test. P values less than 0.05 were accepted as statistically significant. The dependent variable in multivariate models was the presence of culture-positive dermatophytic infection. Odds ratios with 95% confidence intervals (CI 95%) were calculated from the coefficients.

RESULTS

A total of 8122 children, including 4,032 (49.6%) boys and 4,090 (50.4%) girls, with a mean age of 10.61 ± 2.41 (range 5-16) were examined. Nine fingernail and 143 toenail scrapings were taken from children clinically having onychomycosis. The mean age of these 152 children (73 boys and 79 girls) was 11.9 ± 2.2 years (5-16 years). In fingernails, 6/9 (66.6%) and 3/9 (33.3%) patients were diagnosed as DLSO and PSO respectively. In toenails, DLSO was the most frequent clinical diagnosis (114, 73.6%), followed by PSO (16, 10.5%), SWO (4, 2.6%), TDO (6, 3.9%), endonyx (3, 1.9%) [Table 1]. Paronychia was determined in 14 patients with DLSO. Discoloration from yellow-brown to black was the prominent clinical sign in all patients. Hyphae or spores were seen in 65/152 (42.8%) scraping materials by direct microscopy and cultures were positive in 27/65 (41.5%). Onychomycosis were detected in 27/152 (17.8%) patients by isolation. The prevalence of culture-positive onychomycosis was 0.33% (27/8122). There were no fungal KOH-positive or culture-positive cases from fingernails. Toenails were affected in all of the fungal culture-positive cases. Dermatophytes (62.9%) occurred more commonly than yeasts (37.1%) in culture-positive onychomycosis cases. The most common agents in the DLSO were Trichophyton rubrum, Candida spp. and less often, Rhodotorula [Table 2]. Three out of 27 (11.1%) fungal culture-positive cases also had infection of the foot skin caused by the same fungal species, including Trichosporon spp., Candida glabrata and Rhodotorula spp. The culture positive cases were 23/114 in DLSO, 2/16 in PSO, 1/4 in SWO and 1/6 in TDO [Table 1]. Culture results in cases with paronychia were positive in 4/14 due to C. glabrata (3), Candida parapsilosis (1) and these cases also had culture-positive onychomycosis with the same causative agents.

Children aged ≥10 years were more likely to present with onychomycosis (0.55%), compared with the <10 years old group (0.11%) (P = 0.001). Onychomycosis in children having ≥3 siblings (0.45%) was higher than for those having 1-2 siblings (0.04%) (P = 0.002). Onychomycosis in children having unemployed fathers (0.67%) was higher than for those whose fathers were employed (0.21%) (P = 0.003). Onychomycosis in children living in the rural area (0.49%) was found to be more prevalent than those in children living in the urban

<table>
<thead>
<tr>
<th>Clinical type</th>
<th>Clinical diagnosis</th>
<th>Microscopic diagnosis</th>
<th>Number of culture positive cases</th>
<th>Causative agents</th>
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<tbody>
<tr>
<td>DLSO</td>
<td>114</td>
<td>55</td>
<td>23</td>
<td>Trichophyton rubrum (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trichophyton spp. (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trichophyton tonsurans (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Candida glabrata (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhodotorula (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trichosporon (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Candida parapsilosis (1)</td>
</tr>
<tr>
<td>PSO</td>
<td>16</td>
<td>7</td>
<td>2</td>
<td>Trichophyton rubrum (2)</td>
</tr>
<tr>
<td>SWO</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>Trichophyton mentagrophytes (1)</td>
</tr>
<tr>
<td>TDO</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>Trichophyton rubrum (1)</td>
</tr>
<tr>
<td>Endonyx</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td>65</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

DLSO: Distal and lateral subungual onychomycosis, PSO: Proximal subungual onychomycosis, SWO: Superficial white onychomycosis, TDO: Total dystrophic onychomycosis
area (0.25%) \( (P < 0.001). \) Onychomycosis in children living in a house with \(<3\) rooms (0.73%) was higher than for those living in a house with \(\geq 3\) rooms (0.27\%) \( (P = 0.014). \) Onychomycosis in children wearing rubber shoes (0.64\%) was higher than for those wearing non-rubber shoes (0.10\%) \( (P < 0.001). \) There was no statistically significant association between onychomycosis and sex, parent’s education, mother’s occupation, animal husbandry, family income, frequency of having a bath or sock changing.

Age, father’s occupation, number of siblings and rooms were found as potential risk factors for onychomycosis in multivariate logistic model \( [\text{Table 3}] \).

**DISCUSSION**

Onychomycosis is considered among the most common nail diseases in childhood along with eczema, psoriasis, lichen planus, onychodystrophy, alopecia areata and genodermatoses.\(^{[6,14]}\) Dystrophic nails must alert the clinician to the possibility of onychomycosis and should be differentiated from other acquired and congenital conditions.\(^{[15]}\) To our knowledge, this is the first comprehensive study of onychomycosis performed in children living in rural and urban areas in central Anatolia, Turkey. In our study, the overall prevalence of onychomycosis was 0.33\% and \( T.\) rubrum was the most prominent isolate as dermatophytes and \( C.\) glabrata as yeast. Our study also showed that age, parent’s occupational status, number of siblings and rooms were important factors for the frequency of onychomycosis.

The prevalence of onychomycosis is low in children. Studies from North-America and Europe reported the prevalence of onychomycosis as 0.44\% and 0.6\% in children less than 18 years of age.\(^{[16,17]}\) The prevalence of onychomycosis in primary school children of Israel and Spain were reported as 0.87\% and 0.15\%, respectively.\(^{[17,18]}\) Two separate studies conducted in Turkey demonstrated the prevalence of onychomycosis as 0.1\% and 0.08\%, respectively.\(^{[6,19]}\) The prevalence of onychomycosis was very low in our study, similar to previous literature.

In the 1950s, epidemiological studies performed in Turkey reported that the most prevalent causative isolate was \( E.\) floccosum.\(^{[20]}\) However, \( T.\) rubrum was detected as the main pathogen for onychomycosis in this study, which was similar to that in Turkey, India, Western United States, Northern and Southern Europe and was different from that in Africa, supporting the finding that the flora of dermatophytes has recently changed.\(^{[5,9,19-23]}\) A significant increase in the prevalence of \( T.\) rubrum over the last decades may perhaps be due to the greater availability of fungi in the environment and in adults after prolongation of life accompanied by various diseases facilitating the transfer of fungi to children.\(^{[11,18,23]}\)

Yeasts can cause onychomycosis and mixed infections with dermatophytes are also possible.\(^{[24]}\) Reports of onychomycosis caused by \( C.\) spp. in children are less than those caused by dermatophytes. Although \( C.\) albicans and \( C.\) parapsilosis are two frequently isolated species, we found that the dominant causative agent for onychomycosis from yeast was \( C.\) glabrata, followed by \( R.\) and \( T.\) \(^{[1]}\) A study reported that \( T.\) was the most common causative agent for onychomycosis in children living in the West of Turkey.\(^{[6]}\) Diagnosing children

---

**Table 2: Prevalence of causative agents in onychomycosis in school children**

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Culture positive ((n))</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatophyte (total)</td>
<td>17</td>
<td>0.2</td>
</tr>
<tr>
<td>( T.) mentagrophytes</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>( T.) tonsurans</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>( T.) spp.</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Yeast (total)</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>( C.) glabrata</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>( C.) parapsilosis</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>( T.) spp.</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>( R.) spp.</td>
<td>3</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Table 3: Multivariable logistic regression analysis of potential risk factors for onychomycosis**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR</th>
<th>95% CI</th>
<th>( P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 10)</td>
<td>4.04</td>
<td>1.51-10.79</td>
<td>0.05</td>
</tr>
<tr>
<td>Number of siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 3)</td>
<td>7.47</td>
<td>1.00-55.6</td>
<td>0.049</td>
</tr>
<tr>
<td>Father’s occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2.38</td>
<td>1.11-5.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of rooms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 3)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;3)</td>
<td>2.80</td>
<td>1.22-6.55</td>
<td>0.015</td>
</tr>
</tbody>
</table>

OR: Odds ratio, CI: Confidence interval
with *Rhodotorula* and *Trichosporon* infections, suggests that these emerging yeasts should also be considered an opportunistic primary causative agent of onychomycosis.[25,26] However, isolation of different causative agents may be a result of variations in geographic and climatic conditions as well as different relevant methodological aspects, such as sample size, source of participants, type of evaluation and definition of onychomycosis.[27]

This study supported that onychomycosis affected mainly toenails in children compared to fingernails. This could be the result of more traumas and using occlusive footwear or tight fitting shoes, which favors occurrence of onychomycosis. We could not show fingernail onychomycosis by microscopic or culture studies. It might be associated with technical issues or inspection of fingernails during hygienic inspections by teachers, causing awareness of any fingernail diseases earlier. Nevertheless, fingernail onychomycosis seems to be very rare in children living in Kayseri.[28-30]

DLSO type could be seen in children and adults and was the most common clinical pattern in our study, in agreement with previous reports.[10,21] It is known that SWO is very rare in children.[13] Similarly, we detected only one case of SWO in our study. Total dystrophic onychomycosis has also been reported very rarely in children probably due to the faster growth rate of nails compared to adults.[1] We detected only one case with TDO caused by *T. rubrum*. Onychomycosis was associated with tinea pedis in three patients (11.1%); although, this association was found as high as 47% in previous studies.[1]

Onychomycosis prevalence is higher in adults than in children and tends to become more common over the years.[10] Our study showed that onychomycosis was 4-fold (CI: 95% 1.51-10.79) more common in children aged ≥10 years than those aged <10 years, in agreement with other studies.[9-11,18] This can be related to increasing usage of occlusive shoes and more sporting activities resulting in more traumas with increasing age.

Pérez-González *et al.*[31] reported male gender as a risk factor for onychomycosis in Spanish children, similar to reports from Turkey.[6,19] The reason for this difference has not been understood very well. Sex may influence susceptibility to some of the fungal infections like onychomycosis.[31] In our study, sex did not seem to be a risk factor for onychomycosis, in contrast to some previous reports.

Although, it was reported that wearing occlusive footwear and excessive sweating of the feet were important factors in tinea pedis, which might be a facilitating factor for onychomycosis, wearing sweating rubber shoes did not seem to be a risk factor for onychomycosis in our study, even though most of the children with onychomycosis proven to be positive by culture were wearing rubber shoes.[32]

It is difficult to compare our results with the findings of other studies because of few investigations assessing the risk factors for onychomycosis. In our study, the prevalence in children living in a house with ≥2 rooms was 2.8-fold (CI: 95% 1.22-6.55) higher compared to those living in a house with ≥3 rooms. A study from Turkey reported more frequent dermatophytic infections in children living in a dormitory, compatible with our results.[19] The prevalence in children having ≥3 siblings was 7.4-fold (CI: 95% 1.0-55.6) more than those having ≤2 siblings, similar to that in literature.[33] The higher prevalence in children living in a small house and having more siblings may be attributable to crowded environment causing close proximity to each other. Having unemployed father increased the prevalence rate by 2.38-fold (CI: 95% 1.22-6.55). All factors mentioned above might cause poor living standards resulting in increase in the prevalence.

In conclusion, although prevalence of onychomycosis in school children in central Anatolia seems very low, onychomycosis is a growing public health concern all over the world. Children having more siblings or unemployed fathers and children living in small house as well as older children should be examined carefully for onychomycosis. Physicians should consider this infection in the differential diagnosis of diseases affecting nails and provide valuable epidemiological data on future efforts for the prevention and treatment of onychomycosis.

**REFERENCES**


Clinical characteristics of adult-onset actinic prurigo in Asians: A case series

Khor Jia Ker, Wei Sheng Chong, Colin Thiam Seng Theng

ABSTRACT

Background: Actinic prurigo (AP) is a chronic, pruritic skin condition caused by an abnormal reaction to sunlight. Aims: The aim of this study is to determine the clinical characteristics of AP in patients attending the National Skin Centre, Singapore, from 1st January 1999 to 30th June 2008. Methods: Cases of AP diagnosed from 1st January 1999 to 30th June 2008 were retrieved from the center’s electronic medical records and analyzed. Results: A total of 11 patients were diagnosed with AP. The mean age at diagnosis was 52 years. There were 9 (82%) Chinese and 2 (18%) Malay patients. Nine (82%) were male and 2 (18%) were female. The most commonly affected areas were the face, forearms, and hands (72%). Phototesting showed reduced minimal erythema dose (MED) to ultraviolet A (UVA) in 5 (46%) patients, both UVA and ultraviolet B (UVB) in 4 (36%) patients and UVB in 1 (9%) patient. Seven (64%) patients reported partial improvement after treatment with a combination of topical corticosteroids and sunscreens. Four (36%) patients received systemic therapy with partial response. Conclusion: Adult-onset AP is more common in the Asian population, with a male predominance. The face, forearms, and hands are the most commonly affected areas. The absence of mucosal involvement is also a distinguishing feature between the Asian and Caucasian population. Close to half of the patients have reduced MED to UVA on phototesting. The prognosis for AP is poor as it tends to run a chronic course with suboptimal response to treatment.

Key words: Actinic prurigo, Asians, photodermatosis, phototest

INTRODUCTION

Actinic prurigo (AP) is a chronic, pruritic skin disease caused by an abnormal reaction to sunlight. AP can occur at any age, but usually begins before 10 years of age and often resolves in adolescence or early adult life. The eruption of AP is characterized by pruritic papules and nodules, which are frequently excoriated. Eczematization, lichenification, and crusting, with secondary infection are often present.[1] Cheilitis and conjunctivitis may also occasionally be present, particularly in native American patients.[2]

AP involves sun-exposed areas, such as the face (eyebrows, malar regions, nose, and lips), neck, V-areas of the chest, extensors of the arms and forearms as well as dorsum of the hands. It has been shown that these patients react to broad-spectrum radiation ultraviolet A (UVA) and ultraviolet B (UVB), but their minimal erythema dose (MED) to UVB and UVA are usually normal.[3]

Adult-onset AP, defined as the onset of AP after 21 years of age, has been reported and this variant is seen more commonly in Asian patients. Cheilitis and conjunctivitis are usually not associated with adult-onset AP.[4]

The aim of this study is to determine the clinical characteristics of patients with AP seen at the National Skin Centre.
Skin Center, a tertiary dermatology center in Singapore, from 1st January 1999 to 30th June 2008.

METHODS

This study was approved by the local ethics review board. Cases of AP diagnosed from 1st January 1999 to 30th June 2008 were retrieved from electronic medical records in National Skin Center. Demographic data, including age, race, gender, occupation, onset and duration of disease, triggering factors, and clinical features were collated. We also reviewed all investigations performed, including blood tests, phototests, patch tests, and histopathology of skin biopsies. The responses to treatment in all patients were recorded.

Phototesting was carried out using the following light sources: A Kindermann slide projector equipped with a 150 W light bulb (Ochsenfurt, Germany) for visible light, a Supuvasun Mutzhas 3000 high-pressure metal-halide source (spectral output 350-450 nm, peak 370-385 nm) (Munich, Germany) for UVA, and a Dermaray M-DMR-100 bank of seven fluorescent bulbs (FL20S E-30/DMR 305 nm, emission spectrum 290-390 nm, peak 305 nm) (Eisai, Japan) for UVB. The patients' buttocks were exposed to increasing doses of UV radiation. For UVA, radiation doses ranged in geometric progression from 25 J/cm² to 100 J/cm² (irradiance 24 mW/cm² at 21 cm distance) and for UVB, 30-200 mJ/cm² (irradiance 1 mW/cm² at 30 cm distance). The patients' inner forearms were exposed to visible light emitted from the slide projector placed at a distance of 10 cm. The presence of wheals elicited by visible light, UVA or UVB were determined 20 min later and recorded. The MED responses for UVA and UVB were read at 24 h and the smallest dose to achieve "just perceptible erythema" is taken as the MED. For our local population and MED reading of less than 100 J/cm² to UVA and 100 mJ/cm² to UVB is considered abnormal. Monochromatic phototesting is not available at our center.

RESULTS

A total of 11 patients were diagnosed to have AP from 1st January 1999 to 30th June 2008 [Table 1]. Three of the patients had occupations with a significant sun exposure (patients 7, 8 and 11). There were 9 males (82%) and 2 females (18%). The mean age of presentation was 52 years (range: 28-72 years). Nine patients (82%) were Chinese and 2 (18%) were Malay. Two patients (18%) had a history of atopy and 2 (18%) had a family history of atopy.

Patients typically presented with excoriated papules and nodules, often with areas of lichenification [Figures 1 and 2]. In our series, the most commonly affected areas were the face, forearms and hands as shown in 8 out of 11 patients (73%). This was followed by the legs in 7 patients (64%), neck in 6 (55%), arms in 5 (45%), V of the chest and trunk in 4 patients (36%). Only 3 patients (27%) had papules on the scalp, ears, and feet. None of the 11 patients had conjunctivitis or cheilitis.

The mean duration of disease at presentation was 6 years, with a range of 5 months to 33 years. The mean age at onset was 45 years (range: 28-66 years). Only 4 patients (36%) were aware that their lesions were photoaggravated. One patient reported a flare of his itchy rashes an hour after sun exposure with improvement in itch when he was in the shade. In the remaining three patients, their symptoms were aggravated by sun exposure and persisted even when sun exposure ceased. All patients had Fitzpatrick's skin type IV.

Urinary and blood porphyrin screen were performed in 6 patients (55%) with negative results. Anti-nuclear antibodies were performed in 9 patients (82%). All had negative results except for 1 patient who had a low positive titer of 1:100. Tests for human immunodeficiency virus were not performed.

Phototesting was performed in the majority of patients (91%). The MED to UVA was decreased in 5 patients (46%), UVA and UVB in 4 (36%), and UVB in 1 patient (9%). None of the patients had a positive response to visible light. Photo patch test was performed in 1 patient with a negative result.

Four patients (36%) had skin biopsies taken from lesional skin. One biopsy showed mounds of parakeratosis, acanthosis, and slight basal layer hyperplasia. The dermis had increased superficial perivascular lymphocytic infiltrates. Three other biopsies showed non-specific changes.

All patients were treated with a combination of sunscreens and potent topical corticosteroids. Some patients had taken oral antihistamines with minimal
Table 1: Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Sun exposure at work</th>
<th>Age of onset</th>
<th>Duration of disease</th>
<th>Areas affected</th>
<th>Medical history</th>
<th>Drug history</th>
<th>Phototest results (J/cm²)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>Male</td>
<td>Malay</td>
<td>Unknown</td>
<td>28</td>
<td>6 months</td>
<td>Dorsum of hands</td>
<td>Nil</td>
<td>Nil</td>
<td>Not done</td>
<td>Sun protection, topical corticosteroids</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>Male</td>
<td>Chinese</td>
<td>No</td>
<td>66</td>
<td>5 months</td>
<td>Face, ears, dorsum of hands</td>
<td>Bell's palsy</td>
<td>Traditional Chinese medicines</td>
<td>UVA: 75, UVB: 50</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>Male</td>
<td>Chinese</td>
<td>No</td>
<td>30</td>
<td>5 months</td>
<td>Face, neck, dorsum of hands</td>
<td>Nil</td>
<td>UVA: 75, UVB: &gt;140</td>
<td>Sun protection, topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>Male</td>
<td>Chinese</td>
<td>No</td>
<td>28</td>
<td>33 years</td>
<td>Face, V of neck, arms, dorsum of hands, legs</td>
<td>(i) Asthma, (ii) ulnar nerve palsy, (iii) retinal detachment, (iv) Barrett's oesophagus</td>
<td>Simvastatin, omeprazole, hydrochlorothiazide</td>
<td>UVA: 25, UVB: 40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>Male</td>
<td>Malay</td>
<td>No</td>
<td>40</td>
<td>2 years</td>
<td>Forearms, hands, knees, thighs</td>
<td>Nil</td>
<td>UVA: &gt;140, UVB: 60</td>
<td>Sun protection, topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>Male</td>
<td>Chinese</td>
<td>Unknown</td>
<td>66</td>
<td>16 years</td>
<td>Scalp, dorsum of hands</td>
<td>Diabetes mellitus</td>
<td>UVA: Low, UVB: Low</td>
<td>Sun protection, topical and intralesional corticosteroids, antihistamines, topical pimecrolimus (face), azathioprine, cyclosporin, PUVA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Male</td>
<td>Chinese</td>
<td>Yes</td>
<td>40</td>
<td>3 years</td>
<td>Face, V of neck, hands</td>
<td>Nil</td>
<td>UVA: 75, UVB: 105</td>
<td>Sun protection, topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>Female</td>
<td>Chinese</td>
<td>Yes</td>
<td>48</td>
<td>6 years</td>
<td>V of neck, forearms, arms</td>
<td>Nil</td>
<td>UVA: 75, UVB: 40</td>
<td>Sun protection, topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>Female</td>
<td>Chinese</td>
<td>No</td>
<td>48</td>
<td>2 years</td>
<td>Face, V of neck, forearms, shins</td>
<td>Hypertension</td>
<td>Lisinopril</td>
<td>UVA: 50, UVB: &gt;90</td>
<td>Sun protection, topical corticosteroids</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>Male</td>
<td>Chinese</td>
<td>No</td>
<td>53</td>
<td>1 year</td>
<td>Forearms, arms, thighs, legs</td>
<td>Hypertension</td>
<td>Atenolol, nifedipine</td>
<td>UVA: 50, UVB: 120</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>Male</td>
<td>Chinese</td>
<td>Yes</td>
<td>51</td>
<td>10 months</td>
<td>Face, scalp, neck, forearms, hands</td>
<td>(i) Hypertension, (ii) hyperlipidemia, (iii) gout, (iv) renal impairment</td>
<td>Allopurinol, hyzaar</td>
<td>UVA: 25, UVB: &gt;140</td>
<td>Sun protection, topical and oral corticosteroids, antihistamines, azathioprine-Then defaulted</td>
</tr>
</tbody>
</table>

UVA: Ultraviolet A; UVB: Ultraviolet B
or no improvement. Four patients (36%) received systemic therapy, including oral prednisolone, chloroquine, thalidomide, dapsone, azathioprine, cyclosporine, photochemotherapy with psoralens with ultraviolet A (PUVA) and UVA, and UVB phototherapy.

Treatment details of the 4 patients who received systemic therapy are elaborated below. Patient 4 was initially treated with chloroquine 200 mg 3 times a day for 2 months. However, this was stopped because of visual disturbances. He was then treated with oral prednisolone for more than a year. Thalidomide was added, starting at 100 mg daily and gradually reduced to 50 mg. As the lesions improved, prednisolone was tapered off. He relapsed 15 months later and thalidomide was restarted at 200 mg daily with good disease control. Thalidomide was continued for the next 3 years. He was subsequently treated with dapsone for a few months without improvement, and he was switched to azathioprine 50 mg daily, with gradual dose increment to 150 mg daily for 7.5 months. He responded well, but azathioprine was eventually stopped due to gastrointestinal side-effects and headache. Patient 6 was treated with azathioprine for a few months, but this was stopped due to side-effects. He was then switched to cyclosporine without improvement. The patient subsequently underwent PUVA therapy for 6 months with good results. Treatment was then changed to intralesional triamcinolone acetonide injection (10 mg/ml) and topical pimecrolimus on the face. Patient 10 was started on narrowband UVB phototherapy, but with minimal improvement. Patient 11 was treated with azathioprine 50 mg daily and prednisolone 40 mg daily, but he was irregular for follow-up visits.

These patients were followed-up for a mean duration of 48 months (range: 1 month to 20 years). Treatment could reduce the intensity of itch in most patients, achieving a partial improvement in symptoms. However, none of the patients achieved complete remission.

**DISCUSSION**

AP is an immunologically mediated photodermatosis. It is well-reported in the American Indian population, and affected individuals may have a genetic predisposition. Studies have reported a strong association between AP and the human leukocyte antigen (HLA)-DR4 allele, particularly subtype DRB1 * 0407, which has been reported in a number of studies. In contrast, there have been no HLA associations with polymorphous light eruption, which is a more common photodermatosis. The association between AP and HLA typing was not previously reported in the Asian population and as such, HLA typing was not performed in this series.

The relevance of an atopic history in AP is unknown. However, a personal or family history of atopy has been reported. In our case series, 18% of patients had either a personal or family history of atopy, which was comparable to the general population.

Akaraphanth et al. and Lestarini et al. described adult-onset AP as being more common in the Asian population as opposed to the American population where AP usually starts in childhood. Adult-onset AP was also associated with a less favorable prognosis due to persistence of lesions. Our findings in this
case series corroborate with previous studies in Asian populations, with a mean age at onset being 45 years and mean disease duration of 6 years, and a patient even had AP for up to 33 years.

There was a male predominance in our series with a ratio of 4.5:1. This is in contrast to findings by Ross et al.\[13\] in an Australian photobiology unit where there was a female preponderance.

Magaña et al.\[14\] reported that mucosal involvement was frequently associated with AP. In a cohort of 102 mestizo children, labial, and conjunctival mucosal lesions were found in 60% and 30% respectively. In another study by Ross et al.,\[13\] cheilitis was found in 24% of Caucasian patients with AP. However in the Asian population, mucosal involvement was present in only 3% of cases in a study by Akaraphanth et al.\[4\] In our series, none of the patients had cheilitis or conjunctivitis, and this again differentiates the characteristics of AP between the Caucasian and Asian population.

Pruritus in AP is intense and chronic. This leads to chronic scratching, which in turn manifests as erythematous papules with crusts, excoriations, and lichenified plaques,\[15\] which may become secondarily infected. These typical manifestations were seen in our patients in a photo-distributed manner on the face, forearms, dorsum of hands and legs.

Phototesting in AP may show a reduction in MED to UVA, UVB or a combination of both.\[16\] In a series of 20 Australian patients, Crouch et al.\[17\] reported abnormal phototests in 60% of patients with AP. Forty percent of patients had a reduced MED to UVA and the remaining 20% had reduced MED to both UVA and UVB. However, in the United Kingdom, Grabczynska\[18\] found that 30% of patients had a decreased MED to UVB, 25% to both UVA and UVB, and only 5% of cases with a decreased MED to UVA. In our series, all AP patients who were tested had abnormal phototests. Results were similar to those of Crouch et al.,\[17\] with close to half of the patients having reduced MED to UVA, 36% to both UVA and UVB and 9% to UVB alone.

Histology of lesional skin in AP is usually not helpful towards the diagnosis as findings are relatively non-specific.\[13\] However, Hojyo-Tomoka et al.\[19\] reported that AP has distinct histopathologic characteristics with hyperkeratosis, regular acanthosis, and dense infiltrates in the superficial dermis, composed mainly of lymphocytes. The biopsy from one of our patient showed similar findings to the above.

AP is a recalcitrant condition and treatment should be tailored to the individual patient. Essential points in management would include sun protection measures such as sun avoidance, protective clothing against ultraviolet radiation and broad-spectrum sunscreens. There is a paucity of treatment algorithms and of the numerous treatment modalities that have been utilized, thalidomide has proven its efficacy in most patients\[20-23\] and appears to be superior when compared to other treatment options such as antimalarials, beta-carotene, antihistamines, azathioprine, cyclosporine, topical or systemic corticosteroids and phototherapy. However, adverse effects such as peripheral neuropathy and teratogenicity limit its use.

Our patients experienced partial improvement with topical and systemic treatments, but none achieved complete remission. Lane et al.\[24\] reported that 35% of his patients found no relief from any treatment and late-onset AP is less likely to improve with time. Only 17% of his patients improved within 5 years from the time they were first seen.

CONCLUSION

AP is an uncommon photodermatosis. The adult-onset variant of AP is more common in Asians compared to the Americans. A male predominance was seen in our series, in contrast to a female predominance world-wide. An atopic history was also not found to be significant. The absence of mucosal involvement in this series is another distinguishing feature between Asians and Caucasians. Close to half of the patients have a decreased MED to UVA alone on phototesting, consistent with previous reports. Treatment remains challenging and prognosis is guarded, with a chronic course of disease to be expected.

REFERENCES


Use of fine needle aspirate from peripheral nerves of pure-neural leprosy for cytology and PCR to confirm the diagnosis: A pilot study

Abu Hena Hasanoor Reja, Abhishek De, Supratik Biswas, Amitabha Chattopadhyay, Gobinda Chatterjee, Basudev Bhattacharya, Aarti Sarda, Ishad Aggarwal

ABSTRACT

Background: The diagnosis of pure neural leprosy (PNL) remained subjective because of over-dependence of clinical expertise and a lack of simple yet reliable diagnostic tool. The criteria for diagnosis, proposed by Jardim et al., are not routinely done by clinicians in developing country as it involves invasive nerve biopsy and sophisticated anti-PGL-1 detection. We conducted a study using fine needle aspiration biopsy (FNAC) coupled with Ziehl Neelsen staining (ZN staining) and Multiplex- Polymerase Chain Reaction (PCR) specific for M. leprae for an objective diagnosis of pure neural leprosy (PNL), which may be simpler and yet reliable. Aim: The aim of the study is to couple FNAC with ZN staining and multiplex PCR to diagnose pure neural leprosy patients rapidly, in simpler and yet reliable way. Methods: Thirteen patients of PNL as diagnosed by two independent consultants were included as case, and 5 patients other than PNL were taken as control in the study. Fine needle aspiration was done on the affected nerve, and aspirates were evaluated for cytology, ZN staining and multiplex-PCR. Results: Out of the 13 cases where fine needle aspiration was done, M. leprae could be elicited in the nerve tissue aspirates in 5 cases (38.4%) with the help of conventional acid-fast staining and 11 cases (84.6%) with the help of multiplex PCR. On cytological examination of the aspirates, only 3 (23%) cases showed specific epithelioid cells, whereas 8 (61.5%) cases showed non-specific inflammation, and 2 (15.3%) cases had no inflammatory cells. Conclusion: Our study demonstrates that in the field of laboratory diagnosis of PNL cases, FNAC in combination with ZN staining for acid-fast bacilli (AFB) and Multiplex-PCR can provide a rapid and definitive diagnosis for the majority of PNL cases. FNAC is a less-invasive, outdoor-based and simpler technique than invasive nerve biopsy procedure. Thus, this study may enlighten the future path for easy and reliable diagnosis of PNL.

Key words: Acid-fast bacilli, fine needle aspiration cytology, polymerase chain reaction, pure neural leprosy

INTRODUCTION

Leprosy patients lacking skin lesions, but showing involvement of one or more nerves, are afflicted with pure neural leprosy (PNL). On an average, PNL accounts for 5-17.7% of all leprosy cases and is particularly difficult to diagnose as acid-fast bacilli are usually not found in the skin smear or the histological section of nerves.[1] In the absence of a simple non-invasive and sensitive test, the diagnosis of PNL remains clinical and subjective.

Although no such specific diagnosis tool is being put forward neither by any international body nor by any national body with a high specificity and sensitivity, so far some are with high sensitivity and some with high specificity. Hence, combining various tests may improve
the precision of diagnostic procedure of PNL. The gold standard for PNL diagnosis is so far considered as the histopathological examination of a peripheral nerve biopsy. Even so, the detection of bacteria is difficult and histopathological finding may be non-specific. Furthermore, nerve biopsy is an invasive procedure and that is only possible in specialized centers.\[^2\]\ Moreover, as leprosy commonly involves important motor or mixed nerves like ulnar, median, common peroneal nerve, which are unsafe for biopsy even when it is done by an expert. Again nerve biopsy is often unproductive even if it is performed from the relatively safer sural or radial cutaneous nerve.\[^3\]\ To address this issue, recently fine needle aspiration cytology (FNAC) of the affected nerves has emerged as an alternative method of diagnosis.\[^4,5\]\ Previously, in an approach to diagnose PNL, Jardim \textit{et al.} proposed a diagnostic criteria, which involved nerve biopsy, cytology, Polymerase chain reaction (PCR), and estimation of anti-phenolic glycolipid – 1 (anti PGL – 1).\[^6\]\ However, these criteria remained widely unpopular in this part of the world as it involves highly skillful invasive nerve biopsy and sophisticated anti-PGL 1 detection.

With this background, this study is aimed to find out the effectiveness of combining FNAC with cytology, ZN staining and multiplex PCR technique in early, rapid, simpler and possible accurate diagnosis of PNL. As these investigations are safe, ethical, sensitive and do not involve delaying nerve biopsy, we presumed that this study may enlighten the future path for rapid and early and objective diagnosis of PNL.

\section*{METHODS}

\subsection*{Patient selection criteria}
Thirteen clinically suspected cases of PNL were included in the study after obtaining a written informed consent form. The clinical diagnosis was done by two independent experienced dermatology consultants. For clinical diagnosis, definition of PNL was taken as thickening and/or tenderness of a peripheral nerve commonly involved by leprosy with sensory and/or motor functional impairment along the distribution of same nerve. These patients did not have any skin changes suggestive of leprosy.

Patients who were diagnosed by both the clinicians independently as cases of PNL were included in a group designated as “Possible PNL.” Others who were diagnosed as PNL by one observer and non-PNL by the other observer were included in a group designated as “Doubtful PNL.” The presence of “Doubtful group” even in a regional highest referral center like ours, shows that there is an element of subjectivity even amongst the most experienced and skilful dermatologists. Patients who had no clinical sign of Hansen neuropathy, but had easily identifiable ulnar nerve, were included as the “Control group,” provided they signed the informed consent form.

\subsection*{Nerve conduction study}
All the patients were subjected to nerve conduction study (NCS) as per the standard protocols of our hospital in the department of neurosciences.

\subsection*{Fine needle aspiration}
Fine needle aspiration (FNA) was done as described by Theuvenet \textit{et al.},\[^7,8\]\ and aspirates were subjected to cytological examination with Giemsa and ZN staining.

\subsection*{Extraction of DNA from the FNA samples and multiplex PCR}
Genomic DNA was extracted from a portion of the FNA sample aspirates, collected aseptically with the standard precautions from ulnar nerve of study subjects by standard Phenol Chloroform method after proteinase-K digestion as described by Banerjee \textit{et al.}[^9]\ Multiplex PCR

A multiplex PCR for the rapid diagnosis of \textit{M. leprae} was performed as per Banerjee \textit{et al.}[^10]\ based on the following oligonucleotide primers sets:

1. The repetitive sequence of the \textit{M. leprae} DNA reported by Han \textit{et al.},[^11]\ is very specific to \textit{M. Leprae} and not present in 20 other mycobacterial species other than \textit{M. Leprae}. (Primer LR1 and LR2)[^12] as shown in Table 1.

2. A region flanking entire 21TTC repeat sequences, specific for multibacillary leprosy (MB) designed by Shin \textit{et al.}[^12]\ The specificity and sensitivity of the primers: LR1 and LR2 and TTC-A and TTC-B had been already established in our earlier studies.[^10]

Briefly, 100 ng genomic DNA was amplified with Ampli \textit{Taq} Gold, (Applied Biosystems, Inc. [ABI], Foster City, CA) in PCR reaction mixtures, containing 1x PCR buffer (Applied Biosystems), 2 mM MgCl2, 0.25 mM each dNTP, 20 picomoles primers LR1 and LR2 and TTC-A and TTC-B. The primer sequences, primer annealing temperature (Ta°C), and PCR
product sizes are given in Table 1. The PCR reactions were performed in the following conditions: 95°C for 4 minutes, followed by 35 cycles of 95°C for 1 min, Ta° for the internal control as given in Table 1 for 1 min, 72°C for 1 min, and finally elongated at 72°C for 10 minutes. The amplified products were separated by electrophoresis on 2% agarose gel stained with 0.5 mg/mL ethidium bromide and visualized and photographed under a UV transilluminator.

**RESULTS**

The study included a total of 13 cases as “Study group” and 5 cases as “Control group.” Out of the 13 cases, 9 patients were suggested as Hansen neuropathy by at least one of our two observers and were included in “Probable PNL” group, and 4 were included in “Doubtful PNL” group as per inclusion criteria of our study. Out of the 5 patients in “Control group” 1 patient had diabetic neuropathy and the other 4 patients were daily laborer, among which 1 patient had traumatic nerve injury with easily noticeable and identifiable right ulnar nerve.

Out of the 13 cases as in Table 2, 12 patients were male and 1 patient was female within an age group of 15-45 years. Ten patients had both sensory and motor nerve involvement with 3 of them having grade 1 and 7 having grade 2 deformity as given in Table 2, whereas 3 patients had only sensory nerve involvement. None of the patients showed any sign of reactions.

On nerve conduction study (NCS) as shown in Table 2, out of the 4 “Doubtful PNL,” 2 patients had normal NCS and other 2 patients had deranged NCS. However, all 9 “Probable PNL” cases showed some form of defective nerve conduction. Eleven patients who showed abnormal NCS, all showed features of axonopathy, whereas 1 patient also had features of associated demyelinating neuropathy. On combining clinical and neurological findings, we had 11 patients with features of neuropathy, of which 7 had mononeuropathy and 4 had polyneuropathy.

FNAC of all the 9 “Probable PNL” patients showed presence of inflammatory cells in nerve aspirates, whereas out of the 4 “Doubtful PNL,” only 2 cases

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**Table 1: Tm value and primer sequences and used in multiplex PCR**

<table>
<thead>
<tr>
<th>Name of the primer</th>
<th>Primer sequences (5'→3')</th>
<th>Tm value</th>
<th>Product size</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR 1</td>
<td>CGG CCG GAT CCT CGA TGC AC</td>
<td>58°C</td>
<td>372 bp</td>
</tr>
<tr>
<td>LR 2</td>
<td>GCA CGT AAG CTT GTC GGT GC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTC A</td>
<td>GCA CCT AAA CCA TCC CGT TT</td>
<td></td>
<td>201 bp</td>
</tr>
<tr>
<td>TTC B</td>
<td>CTA CAG GGG GCA CTC AGC TC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

bp: Base pair, PCR: Polymerase chain reaction

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**Table 2: Clinical, neurophysiological and FNAC outcome data**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Nerve involvement</th>
<th>Nerve type</th>
<th>Def</th>
<th>Rxn</th>
<th>Clin. diag.</th>
<th>Grp</th>
<th>Nerve conduction study</th>
<th>FNA study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obs 1</td>
<td>Obs 2</td>
<td>Nerve involve</td>
<td>Type</td>
</tr>
<tr>
<td>M</td>
<td>24</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Axon</td>
</tr>
<tr>
<td>M</td>
<td>25</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt Ulnar and Lat. Pop</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td>Rt Ulnar and Lat. Pop</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt Ulnar and Lat. Pop</td>
</tr>
<tr>
<td>M</td>
<td>30</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G1</td>
<td>Neg</td>
<td>Y</td>
<td>N</td>
<td>Doubt</td>
<td>Lt. Ulnar and Rt. Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>31</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt. Ulnar and Lt. Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>27</td>
<td>Rt and Lt Ulnar</td>
<td>S</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Lt. Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>37</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G1</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt. Ulnar</td>
</tr>
<tr>
<td>F</td>
<td>15</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>N</td>
<td>Doubt</td>
<td>Rt. Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>26</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt. Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>35</td>
<td>Rt Ulnar</td>
<td>S</td>
<td>G2</td>
<td>Neg</td>
<td>N</td>
<td>Y</td>
<td>Doubt</td>
<td>Rt Ulnar</td>
</tr>
<tr>
<td>M</td>
<td>28</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>N</td>
<td>Y</td>
<td>Doubt</td>
<td>Lt Ulnar and Lat.Pop</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Lt Ulnar and Lat.Pop</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>Rt Ulnar</td>
<td>S/M</td>
<td>G2</td>
<td>Neg</td>
<td>Y</td>
<td>Y</td>
<td>Prob.</td>
<td>Rt Ulnar</td>
</tr>
</tbody>
</table>

showed inflammatory infiltrate and the rest had no signs of inflammation. However, out of the 11 patients, who had inflammatory aspirates, only 3 had presence of epithelioid cells, whereas all others had non-specific inflammation like neutrophils and lymphocytes. None of our patients had presence of foamy macrophages in their nerve aspirates as given in Table 2.

In case of ZN staining of the nerve aspirate as in Figure 1, out of the 13 cases, we found 5 cases positive for the presence of M. leprae, while the rest 8 cases were found negative for AFB as shown in Table 2. All of the 5 patients positive for AFB were within “Probable PNL” group, whereas none of the “Doubtful PNL” showed presence of M. leprae as in Table 3.

Multiplex-PCR when conducted to the aspirations of “Probable PNL” cases showed positive results in all 9 samples. However, out of the 4 “Doubtful PNL,” only 2 cases were found positive and the rest 2 were found negative for the presence of M. leprae as shown in Table 2. Out of the 9 patients, who showed positive PCR, 4 cases showed positive bands for both 372 bp and 210 bp, whereas the rest 5 cases showed positive band only for 201 bp as shown in Figure 2. The 2 “Doubtful PNL” found positive for multiplex-PCR showed positive band only for 201 bp.

In case of “Control group,” all 5 patients with easily identifiable nerves were found negative for PCR, ZN staining, and FNAC. Among them, 1 patient had diabetic neuropathy and the rest 4 were daily laborer with prominent ulnar nerves; among these 4 patients, 1 had traumatic nerve injury. Negative results in control group gave excellent reference for our Multiplex PCR study.

**DISCUSSION**

Incidence of pure neural leprosy in India has been reported to range from 5.5% to 17.7% of all leprosy cases. Though this constitutes a considerably large fraction of total patients of leprosy, diagnosis of PNL has been purely subjective in the absence of a rapid and yet simple less-invasive laboratory investigation. We, in this study, tried to find out a simple yet effective objective diagnostic tool of PNL by combining PCR AFB staining with FNAC.

Electrophysiological studies such as NCS in our patients showed that 11 out of 13 patients in the study group (84.6%) had axonal neuropathy and only 1 (7%) had features of demyelinating neuropathy as given in Table 2. This result correlates well with Jardim et al., whose findings were 91% and 8%, respectively. This simple technique not only confirms the peripheral neuropathy but also could be valuable instrument in choosing appropriate nerve for FNA. However, as axonal neuropathy of peripheral nerves may occur in a number of conditions, it hardly can be valued as an objective diagnosis of leprosy neuropathy.

The cytological study of the FNA can also provide some supportive evidence of leprosy neuropathy. In our study, we preferred FNAC over biopsy as it was minimally invasive procedure, required very little expertise, can be performed in out-patient department and also minimize the risk of neural damage.

Singh et al. from India documented the cytomorphic features of leprous neuritis from nerve aspirates of **Figure 1: Multiplex PCR showing Lane 1: PhiX174 DNA Marker. Lane 2, 4, 7, 8: Shows positive bands for both 372 bp and 201 bp. Lane 3, 5, 6, 9, 10: Shows positive band for 201 bp only. Lane 11: Positive control (Thai 53 strain) Lane 12: Negative control**

**Figure 2: FNAC aspirates subjected to ZN staining (Carbol Fuchsin stained counter stained by Methylene Blue viewed under X100 immersion oil). Arrows showing AFB mostly fragmented**
28 patients. They concluded that the entire spectrum of leprosy is seen in nerve aspirates.[13]

However, Jardim et al. observed, the defining histological criteria for leprosy neuropathy should include the presence of AFB and epithelioid granuloma, and the presence of a non-specific inflammatory infiltrate (mononuclear cells with no differentiation as to Virchow or epithelioid cells) cannot be taken as a specific diagnostic finding of PNL. They documented though presence of non-specific inflammation was observed in about 71% of the patients, only 40% cases had definitive diagnostic features like AFB or epithelioid granuloma or both.[6]

In our study, out of the 13 suspected cases when subjected to FNAC, we found specific epithelioid cells in only 3 (23%) cases, non-specific inflammation in 8 (61.5%) cases, and 2 (15.3%) cases had no inflammatory cells in the aspirates. Similarly, when FNAC aspirates were subjected for ZN staining as shown in Figure 1, only 5 (38.4%) cases had AFB positive as shown in Table 2, whereas all others were AFB-negative. Based on this data, we could confirm 5 (38.4%) cases as PNL when AFB and cytological data were collaborated together as in Table 3. All of these 5 (38.4%) cases were in “Probable PNL” group as shown in Table 3. Moreover, out of the 5 AFB-positive cases, 4 cases were having polyneuropathy while the remaining 1 was having mononeuropathy as shown in Table 4.

Our findings closely matched that of Jardim et al.[6] and a relative low yield in both our studies points out at the limitation of using either cytological findings or AFB staining as sole diagnostic criteria of PNL.

In the recent years, PCR technique has been successful in demonstrating the presence of M. leprae DNA in leprosy patient’s samples.[9] In a study conducted from India, diagnostic sensitivity of PCR was found to be 88% when DNA was extracted from the biopsy samples of skin patches.[14]

Jardim et al.,[6] in their study, used PCR to diagnose cases, in which the clinical and the histopathological data could not confirm PNL. Their findings were consistent with the results of Chemoulli et al. in which PCR in nerve specimens increased the frequency of M. leprae detection.[15] However, till date, the PCR was mostly done from nerve biopsy specimens. Nerve biopsy is an invasive and highly specialized procedure and ethically may not be permitted as routine investigation, especially when done in the important motor or mixed nerves.[16]

We tried to combine relatively less-invasive and simpler FNAC technique and PCR from FNAC aspirate to overcome the above-mentioned challenges. To the best of our knowledge, our study is the first effort to combine these two procedures to suggest a simpler yet effective objective tool for diagnosing PNL.

We also found, 4 out of the 9 PCR-positive cases as shown in Table 2 had positive bands for both 372 bp and 201 bp, suggestive of high load of bacteria in patient as shown in Figure 2; also when compared with NCS, the outcome showed to have a correlation

| Table 3: Number of total cases of different groups diagnosed by combination of different tests |
|--------------------------------------------------|----------------|----------------|----------------|----------------|
| Combination of tests | Individual test outcome | Total number of cases diagnosed of different group |
|----------------|----------------|----------------|----------------|----------------|
| FNAC+ZN staining | FNAC+PCR | Probable PNL | Doubtful PNL |
|----------------|----------------|----------------|----------------|----------------|
|FNAC+ZN staining | 3 | 5 | 0 | 5 | 0 |
|FNAC+PCR | 3 | 0 | 11 | 9 | 2 |

FNAC: Fine needle aspiration cytology, ZN staining: Ziehl Neelsen staining, PNL: Pure neural Hansen, PCR: Polymerase chain reaction

<p>| Table 4: Neuropathy status by correlation of different test outcomes |
|--------------------------------------------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Status</th>
<th>Total number of cases</th>
<th>Number of cases with polyneuropathy by NCS</th>
<th>Number of cases with mononeuropathy by NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>Both 372 bp and 201 bp</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>PCR</td>
<td>Only 201 bp</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>ZN staining</td>
<td>Positive</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

PCR: Polymerase chain reaction, ZN staining: Ziehl Neelsen staining, bp: Base Pair, NCS: Nerve conduction study
with polyneuropathy as shown in Table 4, while the other 7 cases including the 2 “doubtful cases” showed positive band for only 201 bp, suggestive of low bacterial count in patients, and when compared with NCS, the outcome showed to have a correlation with mononeuropathy as shown in Table 4. Hence, PCR from FNAC may also be suggestive of bacterial load and status of neuropathy in the patient body.

Moreover, a widely held belief to confirm diagnosis of doubtful diseases like PNL, one should diagnose the disease first with a sensitive test followed by the occurrence of positive result with a specific test. Hence, it is clear that by combining FNAC with ZN staining for the presence of AFB (Sensitivity 60%) and PCR (Specificity 100%), we could confirm all 9 cases who were in the “Probable PNL” group and 2 out of 4 cases who were in the “Doubtful PNL” group as given in Table 3. Hence, out of 13 cases, 11 (84.6%) cases were successfully diagnosed for PNL as shown in Table 3. Out of the 2 negative cases among the “Doubtful PNL” group, 1 was female, turned out to have osteomyelitis, mal-union, and entrapment neuropathy; she was sent to orthopedics and was treated surgically while the other was an out-patient from the outpatient department of one of the observer who initially diagnose as Hansen, decided to carry with his clinical judgment despite of his negative results and prescribed him with MDT PB.

CONCLUSION

Based on the above discussion, we may conclude that in the field of laboratory diagnosis, FNAC in combination with Ziehl-Neelsen staining for AFB and Multiplex-PCR can provide a rapid, reliable, efficient and definitive diagnosis for the majority of PNL cases. Thus, this study may enlighten the future path for easy and reliable diagnosis of PNL and probably reinforce the leprosy elimination process.

REFERENCES

Ichthyosiform sarcoidosis revisited

Udas Chandra Ghosh, Sudip Kumar Ghosh, Kaushik Hazra, Asish Mondal

ABSTRACT

Cutaneous manifestations of sarcoidosis are present in approximately one-third of the cases. Ichthyosiform lesion is one of the extremely rare cutaneous manifestations of sarcoidosis. It is an uncommon, but specific cutaneous manifestation of sarcoidosis that may precede or appear simultaneously with the diagnosis of systemic sarcoidosis. Approximately 20 cases of ichthyosiform sarcoidosis have been reported in the PubMed database. We report here a case of sarcoidosis with ichthyosiform skin lesions along with central nervous system (CNS) and pulmonary involvement for its rarity and interesting clinical presentation.

Key words: Cranial nerve palsy, cutaneous, ichthyosiform, sarcoidosis

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of an unknown etiology.[1] Cutaneous manifestations of sarcoidosis are present in approximately 25% to 35% of the cases.[2,3] Since the early description of the disease, many reports have documented the protean clinical manifestations of the disorder. Ichthyosiform lesion is one of the extremely rare cutaneous manifestations of sarcoidosis.[3,4] We report herein a case of ichthyosiform sarcoidosis for its rarity, unusual associations, and interesting clinical presentations.

CASE REPORT

A 35-year-old Indian woman presented with a history of gradual onset of pain and swelling of both ankle joints and dryness and scaling of the skin of the lower limbs for the past 6 months. She was suffering from headache for the last one and half months. In addition, she had double vision, deviation of angle of mouth toward the right side, and loss of sensation of the left half of her face for the last 2 weeks. Her ankle pain was progressive in nature and persisted throughout the day. Other joints were not involved, and there was no early morning stiffness. There was no history of any preceding drug intake or any family history of ichthyosiform disorder. The headache was gradually progressive, persistent, throbbing in character, and associated with photophobia and nausea. Diplopia was more in the left lateral gaze. There was no loss of smell or taste sensations, hearing loss, tinnitus, difficulty in swallowing, altered sensorium, convulsion, fever, weight loss, or cough. There was no significant past history of medical illness. Her menstrual history, bladder and bowel functions, sleep, and appetite were normal.

Cutaneous examination showed xerosis with fine hyperpigmented, adherent, and rhomboidal scales on both legs [Figure 1]. There was no lesional anesthesia nor any thickening of peripheral nerves. No other mucocutaneous lesion was noted elsewhere in the body. Hair and nails were normal. Systemic examination revealed sensory loss in the distribution of the left Vth cranial nerve, left VIth cranial nerve palsy, and lower motor neuron type of palsy of the left VIIth cranial nerve [Figure 2]. Cranium and spine were...
normal, and there was no sign of meningeal irritation. Ankle joints were swollen and tender.

There were no palpable lymph nodes and systemic examination was otherwise normal. Ophthalmological evaluation did not reveal any abnormality. Computed tomography (CT) scan of brain showed normal brain parenchyma. Magnetic resonance imaging (MRI) of brain revealed enhanced and thickened extra-axial tissue symmetrically distributed in the region of both cavernous sinuses [Figure 3]. The right-sided lesion measured about $20 \times 10 \times 13$ mm and that of the left side measured about $21 \times 08 \times 12$ mm. Chest X-ray (CXR) showed upper mediastinal widening. CT scan of thorax showed enlarged and discrete mediastinal lymph nodes in the right para-tracheal and pre-tracheal regions along with a few small enlarged lymph nodes in the left para-tracheal region.

Mild degree of reticulation due to thickening of intra-lobular septa was seen in the right middle lobe and also in the peripheral aspect of the left lower lobe. Some scattered streaky nodules were also noted in the middle lobe [Figure 4]. Sputum for acid-fast bacilli (AFB) was negative. Mantoux test (5 Tuberculin Units) showed no induration. Ultrasonography of the abdomen was normal.

We did a 4-mm lesional punch biopsy of skin from the ichthyotic lesions on the left leg. Histopathology [Figure 5] revealed mild hyperkeratosis, thinning of granular layer, focal acanthosis, and multiple non-caseating well-formed epithelioid granulomas in the dermis without any infiltration of cutaneous appendages or nerves. Modified Fite staining and periodic acid-Schiff stain (PAS) were non-contributory.

A biopsy specimen of apparently normal-appearing skin showed no histological abnormality. In the background of the clinical presentation (including the ichthyosiform skin lesions) and suggestive histopathology, a presumptive diagnosis of sarcoidosis was made. We did serum angiotensin converting enzyme (ACE) estimation that was markedly elevated.

![Figure 1: (a) Ichthyosiform eruption on leg (b) Close-up showing fine hyperpigmented rhomboidal scales and xerosis](image1)

![Figure 2: Deviation of the angle of mouth toward the right side (due to left-sided facial palsy) and medial convergence of the left eye ball (due to left sixth cranial nerve palsy)](image2)

![Figure 3: MRI scan suggestive of neuro-sarcoïd (marked by the black arrows) around cavernous sinus](image3)

![Figure 4: CT scan thorax shows (a) Reticulonodular pattern, (b) Paratracheal lymphadenopathy (marked by the black arrow)](image4)
Subsequently cerebrospinal fluid (CSF) ACE level also showed gross elevation.

Serum calcium level was normal (8.4 mg/dl). Other laboratory investigations including biochemical panels were non-contributory except mild elevation of transaminase levels.

Based on the clinical and laboratory findings, histopathology, and imaging, a diagnosis of ichthyosiform sarcoidosis along with central nervous system (CNS) and pulmonary involvement was made. Oral prednisolone (60 mg/day) was started. Within a couple of weeks, the patient showed significant clinical and radiological improvement.

DISCUSSION

The diagnosis of sarcoidosis is made based on the compatible clinical, laboratory, or radiological features along with histopathological evidence of non-caseating granuloma and when other potential causes, such as infections and foreign objects are excluded.[5] Sarcoidosis can virtually affect any organ system of our body. It mainly involve the lungs, mediastinal, and peripheral lymph nodes, skin, liver, spleen, eyes, and parotid glands. Less commonly, central nervous system, heart, upper respiratory tract, and bones are involved. As cutaneous lesions can exhibit a wide gamut of different morphologies, cutaneous sarcoidosis is known as one of the great masquerader in dermatology.[6] Skin manifestations of sarcoidosis are classified as “specific” or “nonspecific” depending on the presence or absence of noncaseating granuloma.[2] The common specific lesions include lupus pernio, infiltrated plaques, macular and papular lesions, and subcutaneous nodules. Hypopigmented patches, ulcers, alopecia, verrucous lesions, and ichthyosiform lesions are relatively less common specific manifestations. On the other hand, the commonest nonspecific lesion of sarcoidosis is erythema nodosum.[5]

Acquired ichthyosis has been reported to occur in association with a wide gamut of systemic illnesses. It is known to occur with Hodgkin’s disease, leprosy, drugs, hypothyroidism, lymphosarcoma, multiple myeloma, carcinomatosis, and chronic malnutrition among others.[1,2,7] In these instances, only ichthyosiform change is present histopathologically; microscopic alterations suggestive of or diagnostic of the generalized disease process with which they were related are not present.[2] Ichthyosis-like eruption may develop several months before the diagnosis of generalized sarcoidosis as in the present case.

Biopsy specimens frequently show not only non-caseating granuloma but also epidermal changes, which are consistent with ichthyosis vulgaris and which comprise of ortho-hyperkeratosis and a decreased or absent granular layer.[1]

The diagnosis of sarcoidosis in the present case was supported by the demonstration of well-formed epithelioid granuloma along with ichthyosiform changes in the skin biopsy specimen, negative Mantoux test, markedly raised ACE, hilar adenopathy in CXR, features of lung parenchymal involvement in the CT scan, and features suggestive of neurosarcoid in the MRI brain along with raised ACE level in CSF.

We searched the PubMed and Medline databases with the terms “ichyosiform sarcoidosis.” Less than 20 reports of ichthyosiform sarcoidosis were found. It has been virtually always seen among non-white persons. Out of these, only a few cases have been reported in Indian patient.[6,9] One case of ichthyosiform sarcoidosis without any systemic feature has been reported in a 25-year-old Indian woman.[8]

Another case of ichthyosiform sarcoidosis after chemotherapy for Hodgkin’s disease has been reported in a 36-year-old Indian man.[9] Ichthyosiform sarcoidosis typically presents as asymptomatic, adherent, and polygonal hyperpigmented scales on the lower extremities.[1] The presence of these ichthyosiform lesions correlates well with the
presence of systemic disease. Ninety-five percent of all reported cases of ichthyosiform sarcoidosis have systemic involvement at the time of diagnosis or develop systemic involvement within several months.\(^1,4\) Treatment of sarcoidosis should be tailored to the patient and depends on the organ involvement and stage of the disease. Systemic corticosteroids are the most widely used drug for the treatment of systemic involvement in sarcoidosis. Other treatment options available are hydroxychloroquine, methotrexate, azathioprine, pentoxifylline, thalidomide, cyclophosphamide, cyclosporine, and infliximab among others. Topical steroids maybe considered for the treatment of anterior uveitis and skin lesions.\(^{10}\) The ichthyosiform lesions have been reported to improve to both topical and systemic glucocorticoids.\(^1\)

Association of multiple cranial nerve palsy as a manifestation of neuro-sarcoid along with ichthyosiform skin lesions was an unusual combination of features in our patient. We seek to emphasize the importance of excluding sarcoidosis in any patient with acquired ichthyosis. Furthermore, this case also highlight the importance of skin biopsy in the evaluation of acquired ichthyosis.

REFERENCES

Granulomatous cheilitis with granulomatous vulvitis: A rare association

Srinath M. Kambil, Ramesh M. Bhat, Sukumar Dandakeri, Nelee Bisen

ABSTRACT

Granulomatous cheilitis and granulomatous vulvitis are rare disorders characterized by painless swelling of lips and vulva, respectively. Histopathology of both conditions show non-caseating epithelioid cell granulomas in the dermis. Both disorders have been associated with Crohn’s disease rarely. Occurrence of the two conditions in the same patient is extremely infrequent. We hereby report, the association of granulomatous cheilitis with granulomatous vulvitis in a 30-year-old female.

Key words: Cheilitis, Crohn’s disease, granulomatous, vulvitis

INTRODUCTION

Granulomatous cheilitis is a chronic granulomatous inflammation of the lips of unknown etiology characterized clinically by diffuse, non-tender and soft to firm swelling of one or both lips. The genital counterpart of granulomatous cheilitis is called granulomatous vulvitis, which presents as painless swelling of the vulva. Granulomatous disorders such as metastatic Crohn’s disease, sarcoidosis and mycobacterial infections have to be ruled out when a patient presents with granulomatous cheilitis and/or vulvitis.[1]

CASE REPORT

A 30-year-old woman presented with 10 years history of painless swelling of upper lip, which was intermittent initially, but since last 2 years became progressive and persistent. She also gave 6 months history of painless swelling of lower lip and vulva. Patient was otherwise well and reported no history of facial palsy, gastrointestinal or respiratory symptoms except for recurrent vaginal discharge since the last 10 years. Dermatological examination showed erythematous firm swelling of both lips with the upper lip more affected [Figure 1a]. Genital examination revealed indurated swelling of labia majora with the left side more affected than the right. Few indurated papules and a solitary infiltrated plaque were seen in the groin [Figure 1b]. White watery vaginal discharge was present, which on culture showed peptostreptococci and bacteroides species sensitive to metronidazole. The findings of routine blood work-up including angiotensin converting enzyme level were normal except for hemoglobin level of 9.4 mg/dl and raised erythrocyte sedimentation rate of 126 mm/1st h. Chest X-ray was normal and Mantoux test was negative. Stool examination was normal. Colonoscopy with multiple colorectal biopsies did not show any evidence of Crohn’s disease. Histopathological examination of biopsies taken from upper lip and vulva showed non-caseating epithelioid cell granulomas and mononuclear cell infiltrate in the dermis [Figure 2a and b]. These features were suggestive of granulomatous cheilitis and granulomatous vulvitis. Based on clinical and histopathological features, a final diagnosis of granulomatous cheilitis and granulomatous vulvitis was made. Patient was started on intralesional...
Granulomatous cheilitis with granulomatous vulvitis
triamcinolone acetonide at every 2 weeks interval and oral metronidazole 400 mg twice daily. At 1 month follow up, there was considerable improvement in lip and genital swelling [Figure 3a and b].

DISCUSSION

Granulomatous cheilitis is an uncommon disorder, which presents initially with intermittent swelling and later with persistent swelling of one or both lips and belongs to a larger group of orofacial granulomatosis. It may occur as a part of Melkersson-Rosenthal syndrome, which is a triad of granulomatous cheilitis, facial nerve paralysis and fissured tongue. The cause is not known in majority of cases though in few cases, Crohn’s disease, sarcoidosis, genetic factors, allergy to food additives, vasomotor disturbances and infective factors such as mycobacterium tuberculosis, herpes simplex and apical periodontitis have been suggested. Typical histopathological features consist of epithelioid cell granulomas with langhans giant cell and mononuclear cells though a more banal infiltrate may be seen in early stage. Various treatment options include systemic and intralesional corticosteroids, clofazimine, hydroxychloroquine, antibiotics such as metronidazole, minocycline and roxithromycin, infliximab, thalidomide, methotrexate, fumaric acid esters and tranilast. Cheiloplasty and helium neon laser radiation treatment has been tried in resistant cases. Granulomatous vulvitis is a rare disorder, which is considered as the genital counterpart of granulomatous cheilitis. Both disorders are characterized by persistent labial swelling and non caseating granulomas extending into deep dermis, composed of histiocytes and giant cells, associated with lymphomonocytic infiltrate. Few cases of granulomatous vulvitis have been found to be associated with Crohn’s disease, but in majority of cases the cause is not known. Treatment options include topical, intralesional and oral corticosteroids, antibiotics such as metronidazole and ciprofloxacin, immunosuppressants such as azathioprine and cyclosporine. Salazosulfapyridine, mesalazine and anti-tumor necrosis factor monoclonal antibodies such as infliximab and adalimumab have been used with good results in granulomatous vulvitis associated with Crohn’s disease.

Granulomatous cheilitis and granulomatous vulvitis can occur together in the same patient as in our case, but it is extremely rare. Though in our patient, all
relevant investigations performed to rule out Crohn’s disease, sarcoidosis and tuberculosis didn’t show any positive finding, it is essential to rule out these granulomatous disorders when a patient presents with persistent lip and/or genital swelling

REFERENCES

Follicular Dowling Degos disease: A rare variant of an evolving dermatosis

Saurabh Singh, Sujay Khandpur, Parul Verma, Manoj Singh

ABSTRACT

Dowling Degos disease is a rare, reticulate pigmentary disorder with variable phenotypic expression that manifests as hyperpigmented macules and reticulate pigmentary anomaly of the flexures. Many variants of this condition and its overlap with other reticulate pigmentary disorders have been reported in the literature. We present here two cases of DDD with follicular localization, both clinically and histologically. It was associated with ichthyosis vulgaris in one case. Follicular DDD is an uncommon variant of this evolving dermatosis. Our report supports the possible role for disordered follicular keratinisation in its pathogenesis.

Key words: Dowling Degos disease, follicular Dowling Degos disease, reticulate pigmentary disorders, Dowling Degos disease and ichthyosis

INTRODUCTION

Reticulate pigmentary disorders are a heterogenous group comprising of several inherited conditions that are characterized by reticulate hyperpigmentation and several other cutaneous and extra-cutaneous associations.[1] Dowling Degos disease (DDD) is a rare, autosomal dominant disorder with variable phenotypic expression that manifests as hyperpigmented macules and reticulate pigmentary anomaly of the flexures. Uncommonly, it may involve the scalp, face, wrists and genitalia.[2] Follicular lesions mimicking chloracne and perioral pits, occurring in association with classic disease, have been reported in the literature. The purpose of this report is to describe a true follicular variant of DDD, both clinically and histologically. We seek to highlight this variant and differentiate it from other conditions that manifest as follicular keratotic papules, macules, and pits. Interestingly, one of the cases also had associated ichthyosis vulgaris.

CASE REPORT

Case 1 was a 25-year-old man presented with hyperpigmented macules and pits over face, trunk, and extremities of 15-years duration. The lesions were asymptomatic, but progressive in nature. He developed keratotic papules on face that healed with pitted scars. There was family history of similar lesions in 7 of 8 members (Index case, 5 siblings and mother), but they were not available for examination. Dermatological examination revealed multiple follicular macules and perioral pits, occurring in association with classic disease, have been reported in the literature. The purpose of this report is to describe a true follicular variant of DDD, both clinically and histologically. We seek to highlight this variant and differentiate it from other conditions...
follicular epithelium with increased melanisation at their tips and sides. The interfollicular epithelium was not involved [Figure 1c]. A diagnosis of follicular DDD was made. Because of the prominent follicular nature of lesions, the patient was first prescribed topical tretinoin cream (0.05%) and, subsequently, oral isotretinoin (0.5 mg/kg/day), each for 4-6 weeks without any improvement.

Case 2 was a 19-year-old girl who presented with multiple pitted scars and keratotic papules over face, extremities, and trunk of 14-years duration. The facial scars were cosmetically disfiguring. In addition, she gave a history of recurrent nodular lesions over the back, which healed with depressed scarring. There was no history of acneiform lesions (papules or pustules) preceding the pitted scars. Family history of similar lesions was positive in mother, two of mother’s sisters, and maternal grandfather, of which, only the mother was available for examination. Dermatological examination revealed prominent pitted scars over the face (forehead, nose, malar area, perioral region) and upper back; comedo-like hyperpigmented follicular papules over nape of neck and back; and few inflammatory nodules over the upper back [Figure 2a and b]. Hands and feet were spared and there was no flexural accentuation of lesions. Her mother had hyperpigmented macules and papules located over face, neck, and chest; perioral pitted scars; and grouped hyperpigmented macules and papules over flexures, which were suggestive of DDD. Histopathology from both pitted scar and comedo-like papule in the daughter showed dilated follicular infundibulum, with thin, interconnecting rete-ridges and increased melanisation over their tips and sides. There was complete sparing of interfollicular epidermis. The features matched those of follicular DDD [Figure 2c]. Considering the psychosocial disfigurement caused by the pitted scars, fractional CO2 laser has been planned for the index case.

DISCUSSION

DDD is a reticulate pigmentary disorder with autosomal dominant mode of inheritance, but may occur sporadically. It is characterized by hyperpigmented macules in a reticulate pattern over the flexures. Associated features include comedo-like papules, perioral pitted scars, epidermoid/trichilemmal cysts, chloracne-like manifestation, generalized variant, association with hidradenitis suppurativa, Galli Galli disease and overlap with reticulate acropigmentation of Kitamura (RAPK).

Both the cases were interesting in view of presence of punctate folliculocentric pigmented macules,
pits and comedo-like lesions, extensively involving face, back, extremities and flexures with the absence of characteristic non-follicular flexural hyperpigmentation of DDD.

Bhagwat et al.[9] reported 3 cases of DDD from two families, who had tiny hyperpigmented macules and pits in a generalized distributed, but unlike in our case, all of them also had reticulate hyperpigmentation. The comedo-like papules over face and back in our cases lacked the typical involvement of lateral face and ear, as seen in chloracne. We ruled out familial dyskeratotic comedones that are characterized by large comedo-like papules prominently involving trunk and distal extremities, and sparing the head and neck.[10] Comedonal Darier’s disease, a rare entity characterized by keratotic or nodular lesions over face, scalp, and upper trunk, was excluded because of the absence of associated classic Darier’s nail and palmar features and typical histological findings of corps ronds and grains restricted to follicles.[11] Haber’s disease is now considered distinct from DDD, because it has early-onset rosacea-like eruption on the face, multiple seborrheic keratosis-like lesions on the trunk, especially on the flexures, which show classic features of solid seborrheic keratosis on histology.[11]

Interestingly, the skin biopsies in our patients showed classic changes of DDD strictly restricted to the follicular epithelium. This finding, as far as ascertained, has not been previously mentioned in literature. In a study by Kim et al.[3] on 6 cases of DDD, rete ridge elongation with basilar hyperpigmentation, thinning of suprapillary epidermis and dermal melanosis were the most consistent findings. In addition, one patient also showed horn cysts. In their study, these changes were seen in both epidermis and follicular epithelium, but were more prominent at the infundibular region. Kershenovich et al.[4] reported a case of DDD mimicking chloracne. It shared some similarities to our case in the form of punctate hyperpigmented macules and comedo-like papules over the face, chest and back. Histologically, it showed branching hyperpigmented rete ridges emanating from the sides of cystically dilated follicular infundibula and, unlike in our case, focally also from the surface epidermis.

DDD is caused by loss of functional mutations in the keratin 5 gene. But lately, several reports including the current case, have highlighted the possible role of follicular pathology in its genesis, and the indicators include clustering and punctate nature of the lesions, association with hidradenitis suppurativa, and comedo-like lesions, and prominent infundibular changes on histology.[3,4,6,9] Interestingly, our patient had another inherited keratinizing disorder in the form of ichthyosis vulgaris, which however is known to be caused by filaggrin gene mutation, unrelated to DDD.

In conclusion, a keen and meticulous recording of the clinical and histological features and follow up of DDD is advised in order to further elucidate its pathogenesis and natural course, which would thus help in better understanding and management of this disease.

REFERENCES
INTRODUCTION

Silver—The metal

Silver is a naturally occurring metallic element that has no known physiological or biological function in the human body. It is present widely in the human environment; henceforth, low concentrations are also present in the human body. Normal healthy people have silver levels of <3 μg/L.[1]

Toxicity and metabolism of silver

The ability of a metal to produce toxic effects on body depends on the type of compound/form of the metal, the amount and mode of absorption, its metabolism in the body and the cellular vulnerability to toxic damage.[1,2] Absorption of metallic silver is much less when compared with soluble silver compounds.[1] Silver is absorbed into the body through inhalation, ingestion, intraparenteral through insertion of needles or implantation of medical devices or accidental puncture wounds and through dermal or mucosal contact.[1,2] The percutaneous absorption through intact skin is very low, however, in wounds and burns the absorption increases significantly.[1,3] The metallic and inorganic silver compounds ionize to silver ion on exposure to body fluids, which after absorption in the systemic circulation by ion uptake binds to thiol and proteins ligands such as metallothioneins, albumins and macroglobulins and is metabolized.[1,4]

The acute toxicity due to exposure to large doses of inorganic silver salts such as silver nitrate is similar to corrosive effects leading to irritation of the gastrointestinal tract (if ingested) manifested in the form of epigastric burning, vomiting and diarrhea or respiratory tract irritation (if inhaled), severe toxicity will cause decreased blood pressure and decreased respiration ultimately leading to convulsions and shock.[2,3,5] Instillation of silver nitrate in the renal pelvis or urinary tract for chyluria have been reported to be associated with renal and hepatic failure, acute necrotizing ureteritis, obstructive nephropathy and papillary necrosis.[1] The corrosive effects are likely to be due to the nitrate in the compound rather than by the silver itself.[2] Organic silver compounds such as colloidal silver are less toxic however consumption of large doses of colloidal silver may lead to coma, pleural edema and hemolysis.[3]
The chronic toxicity occurs after prolonged exposure when the absorption of silver exceeds body metabolizing capacity leading to precipitation as inert silver sulfide and/or silver selenide in soft-tissues [1] (with highest concentrations in skin, liver, spleen and adrenal glands). [3] The chronic toxicity is not associated with an irreversible toxic damage to organs or carcinogenicity and the principal clinical manifestation is disfiguring cutaneous pigmentation called argyria or corneal/conjunctival pigmentation called argyrosis. [1]

Several safe limits set up by different regulatory authorities exist for silver depending upon the form of silver and mode of exposure. For occupational exposure a recommended exposure limit of 0.01 mg/m³ in the air for both metallic and soluble compounds of silver and two separate exposure limits of 0.1 mg/m³ for metallic silver and 0.01 mg/m³ for soluble silver compounds are established by The National Institute for Occupational Safety and Health and The American Conference of Governmental Industrial Hygienists respectively. [2] A chronic oral reference dose of 5 µg/kg/day is given by The environmental protection agency. [3] World Health Organization limits are up to 0.1 mg/L for drinking water levels and total lifetime oral intake of 10 g for no observable adverse effect levels. [1] However, it is difficult to determine the lowest dose of silver leading to argyria because various studies have not been able to establish a clear relationship between exposure to silver, blood silver levels or minimal body silver concentrations with early signs of the condition. [1]

Pathogenesis of argyria

The photocatalyzed reaction analogous to developing a photographic film is the underlying mechanism behind the discoloration of argyria seen preferentially in sun exposed areas. [2] Recently, Liu et al. have proposed a conceptual model for pathogenesis of argyria. Sunlight catalyzes the silver complexes in the skin to elemental silver, which spontaneously forms the immobile silver nanoparticles. This is followed by transformations of silver nanoparticles into sulfides and further into selenides or Se/S mixed phases through exchange reactions. [4] In addition, silver also stimulates melanin production thus adding to the discoloration. [2]

CASE REPORT

A total of 4 patients, of these 1 were male and 3 were female presented with insidious onset grey-blue macular shiny pigmentation involving predominantly sun exposed areas [Figures 1 and 2]. Nail involvement (azure lunulae) was observed in two patients [Figure 3] while discoloration of the oral mucosa was present in one patient. The cause of argyria was elucidated to be long-term ingestion of silver coated cardamoms in two and silver coated betel nut in other two [Table 1].
Histopathological examination showed similar features in all patients. The distinctive feature observed was deposition of fine black granules in the basement membrane of eccrine secretory coils [Figure 4], blood vessels wall, around pilosebaceous units and along the elastic fibers of the papillary dermis [Figure 5]. The granules were refractile under dark field microscopy [Figure 6]. Masson-Fontana and Perl’s stain were performed to exclude melanin and hemosiderin granules respectively.

**DISCUSSION**

Silver deposition leading to pigmentation had been recorded as early as 8th century. The term “argyria” was coined by Fuchs in 1840.[5] It was prevalent in 19th and early 20th century.[6]

Argyria can be localized or generalized, depending upon the mode and amount of silver absorbed. Localized argyria is the pigmentation of skin or mucous membranes due to impregnation of silver confined to the site of direct contact.[2] Besides the commonly characterized forms of localized argyria i.e., cutaneous, ocular (argyrosis) and oral cavity (amalgam tattoo), some unusual locations of localized argyria are nasal mucosa,[7] trachea,[8] urinary tract,[9] vagina,[10] and penis.[11] In generalized argyria, the silver is systemically absorbed and is widely deposited in skin, eyes, mucous membranes and nails.[2]

**Etiological factors**

**Occupational**

Silver, apart from its wide usage in jewelry and silverware, has extensive industrial applications including photography, soldering, in batteries, in mirrors to name a few.[2] Silver exposure in miners and other occupations as the cause of argyria, especially generalized, has become less prevalent due to availability as well as enforcement of better protective measures at work place.[2] However, isolated cases of occupational argyria mostly localized[7,12-16] and rarely generalized[17] continue to be recorded. Some interesting reports of occupation related argyria cited

<table>
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<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Clinical features</th>
<th>Cause of silver exposure</th>
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<tbody>
<tr>
<td>1</td>
<td>55 years/female</td>
<td>Blue grey discoloration of face, scalp, neck, forearm, dorsa of hands and nails</td>
<td>Intake of 10-15 silver coated cardamoms per day for 7-8 years</td>
</tr>
<tr>
<td>2</td>
<td>56 years/male</td>
<td>Blue grey discoloration of the face, earlobes, nails and oral mucosa</td>
<td>Intake of silver coated betel nut with tobacco for 20 years</td>
</tr>
<tr>
<td>3</td>
<td>50 years/female</td>
<td>Blue grey discoloration of face with predilection for nose, forehead and pinnae</td>
<td>Intake of silver coated betel nut for 8 years</td>
</tr>
<tr>
<td>4</td>
<td>46 years/female</td>
<td>Blue-grey pigmentation on face involving perioral area, cheeks and temple</td>
<td>Intake of silver coated cardamoms for several years</td>
</tr>
</tbody>
</table>
in the literature include black tears as a result of occupational inhalation of silver,[18] localized argyria in an antique restorer[19] and localized cutaneous argyria in a dental surgeon called as cutaneous amalgam tattoo by the authors.[20]

**Medicinal and therapeutic**

Silver has had medicinal uses since ancient times. Historically, silver nitrate was used for neurological disorders such as epilepsy and tabes dorsalis. In the late 19th and early 20th century, silver compounds and colloidal silver proteins for their antimicrobial, caustic, astringent and hemostatic properties had varied spectrum of usage. Silver compounds were used for treatment or prevention of infectious diseases like gonorrhea including Crede’s method for ophthalmia neonatorum and syphilis, gastrointestinal disorders, oral ulcers, for removal of warts and for bladder irrigation. Silver was also used in allergy and cold remedies, eye drops, nasal sprays, lozenges and antismoking pills.[2,3,5,21] Thus, the medical exposure was the most common source of argyria.[2,3] With the development of antibiotic and better pharmaceutical agents the medicinal use of silver declined.[2,5] In 1999, US Food and Drug Administration prohibited the sale of over the counter (OTC) medications containing silver.[5]

In present day medicine, the use of silver is mainly confined to silver dressings for burns/wound management and in medical appliances.[3,21] The silver dressings have come a long way from silver foils to popular silver sulfadiazine cream to present day nanocrystalline dressings.[3,21] The spectrum of silver based medical appliances has also evolved from silver wire sutures to various other devices such as prosthetic implants, splints, catheters, heart valve, stents, bone cement, dental fillings.[1,21] The incidence of argyria with these forms of applications is low, however, localized argyria has been reported with the use of silver dressings/cream[10,11,22-24] and with the implantation of medical devices.[8,25-27] Rarely generalized argyria has been documented either with prolonged use of silver dressings/cream or application over large body surface area such as in cases of burns, epidermolysis bullosa and venous leg ulcers.[10,28-30]

Recently, there has been a resurgence in the unregulated use of silver in the form of dietary supplements and as a constituent of alternative medicine/home remedies.[2,5] There are hundreds of websites proclaiming the benefits of silver compounds.[2,5,31-33] Most of the reported cases of generalized argyria in the 21st century have been associated with long-term and indiscriminate use of these preparations.[5,6,31-52] It is worth mentioning herein, two reports of familial argyria in members of the same family due to prolonged use of silver containing formulations as a form of alternative medicine.[53,54] Apart from this, localized cases of argyria have also been reported following acupuncture.[55-57]

**Personal and socio-cultural**

Cases of argyria have been associated with certain personal and socio-cultural practices. Examples include argyria associated with the use of mouth fresheners[55,58-60] and sugar coated particles.[61] Silver earrings[62,63] and eyelash dye[64] have led to localized argyria. Generalized argyria cases have been reported in psychiatric illnesses, such as, schizophrenia,[58] somatic delusions,[31,51] schizoaffective disorder[52] and due to chewing of photographic film.[65]

**Environmental and incidental**

Localized argyria has occurred due to chemical explosion,[66] and trauma.[67,68] Contaminated water used in hemodialysis has led to generalized argyria.[69]

**Clinical features**

In general, the macular pigmentation in argyria is slate–grey. It arises insidiously and is asymptomatic. The pigmentation is subtle and goes unrecognized for months and years.[6,32,33,46] It is more pronounced on sun exposed areas including face, neck, [Figure 1] arms and dorsum of the hands.[2] It is often viewed by the patient as persistent tan. However, the clinical morphology and anatomic pattern is sufficiently distinctive as exemplified by our four patients. The shiny quality of pigmentation [Figure 2] and the diffuse pattern is in contrast to brown-black patchy pigmentation of melasma. Mucosal/conjunctival involvement and azure lunulae (nails) [Figure 3] are characteristic attributes of argyria. In our opinion, with knowledge and awareness, argyria can be clinically recognized.

Clinical differential diagnosis of argyria includes other causes of cutaneous discoloration [Table 2]. Generalized argyria can closely mimic metabolic causes of pigmentation, which too are uncommon and only a thorough clinical work-up will allow the correct diagnosis to be arrived at. Generalized argyria has been mistaken for cyanosis in individuals of light skin.[32,41,70] The localized argyria needs to be
distinguished from melanocytic lesions like blue nevi and malignant melanoma. An exhaustive history is necessary for eliciting the mode and duration of silver exposure. At times, the exposure to silver may not be readily apparent as is evident from a reported case of generalized argyria caused by silver element in a tea kettle.  

**Histological features**

Argyria appears as invisible dermatosis under scanning magnification. Diagnostic features seen on high power are characterized by the deposition of uniform fine brown black granules in the basal lamina of the secretory portion of eccrine glands, blood vessel walls and elastic fibers of the papillary dermis. To a lesser extent deposits are also seen in connective tissue sheath surrounding pilosebaceous units, perineural tissues and arrector pili muscles. Dark field microscopy under which the granules are brightly retractile is particularly useful in suspected cases of argyria where the deposits are not evident under light microscopy. In localized argyria an unusual histological finding of yellow brown collagen bundles similar to pseudo-ochronosis has occasionally been described.

Histopathological examination is important to establish the definite diagnosis and to exclude other causes of pigmentation because these have significantly different implications from the management and prognostic point of view. The cutaneous deposits can be histochemically characterized as silver compounds by techniques such as transmission electron microscopy with electron loss spectroscopy or scanning electron microscopy with energy dispersive radiograph microanalysis. However, these techniques are not readily available, in this setting, the specific characteristics and the localization of the silver granules as observed under light microscopy with dark field microscopy can distinguish it from some of the other common heavy metal granules.

**Management**

Cessation of silver exposure and sun-protection with sunscreen are useful for preventing further progression of pigmentation. Various treatment options such as chelation, hydroquinone and dermabrasion are not effective. Recently, Q-switched 1064-nm neodymium-doped yttrium aluminium garnet laser has been reported to be useful for resolving the skin discoloration in argyria.

**Indian perspective**

All the four cases of argyria, described in this article are due to intake of silver coated betel nut/cardamoms. An extensive literature search conducted

### Table 2: Clinical differential diagnosis of argyria

<table>
<thead>
<tr>
<th>Generalized argyria</th>
<th>Localized argyria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Melanocytic lesions</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Blue nevus</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Tattoo</td>
</tr>
<tr>
<td>Ochronosis</td>
<td>Silver (argyria)</td>
</tr>
<tr>
<td>Melanosis</td>
<td>Erythema dyschromicum perstans/lichen planus pigmentosus</td>
</tr>
<tr>
<td>Drug deposition</td>
<td>Melanosis secondary to wide spread melanoma</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Amiadarone</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Metals</td>
</tr>
<tr>
<td>Gold</td>
<td>Mercury</td>
</tr>
<tr>
<td>Bismuth</td>
<td>Arsenic</td>
</tr>
<tr>
<td>Lead</td>
<td>Mercury</td>
</tr>
</tbody>
</table>

### Table 3: Histopathological differentiating features of important heavy metal granules

<table>
<thead>
<tr>
<th>Metal</th>
<th>Granule characteristics</th>
<th>Cutaneous localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver (argyria)</td>
<td>Uniform, brown-black, minute &lt;1 μm, retractile under dark field</td>
<td>Basement membrane of eccrine glands, blood vessel walls and elastic fibers of papillary dermis. To a lesser extent in the connective tissue sheaths of pilosebaceous units, perineural tissue and in arrector pili muscle</td>
</tr>
<tr>
<td>Gold (chryiasis)</td>
<td>Larger, irregular in size, round or ovoid, retractile under dark field, orange red birefringence under poloroscopic examination</td>
<td>Macrophages around blood vessels in upper and mid dermis</td>
</tr>
<tr>
<td>Mercury</td>
<td>Large aggregates of up to 340 μm</td>
<td>Macrophages around blood vessels, along the elastic fibers and free among collagen bundles in upper dermis</td>
</tr>
</tbody>
</table>
with the purpose to identify the reports of argyria pertaining to related forms of exposure yielded five citations,[55,58-61] Interestingly, of these, four are from Japan and one from Taiwan. In four of the citations the cause of argyria is ingestion of mouth freshener “Jintan,”[55,58-60] while in one, argyria is attributed to consumption of silver coated sugar particles.[61] This appears to be a unique cause of argyria due to cultural practice confined to the Asia.

The thin silver leaves called as “Warq” are quite commonly used to coat sweets, cardamoms and betel nut and mouth fresheners. Ash of silver is also widely used in Ayurveda one of the Indian traditional systems of medicine.[73] Silver containing topical medicines are freely available as OTC drugs in India. To the best of our knowledge, this pattern of argyria has not been previously documented from India. Knowing how habit forming is the practice of chewing silver coated mouth fresheners and how widely it is prevalent in India, it comes as a surprise that there are not many more reported cases of argyria. We are tempted to speculate that argyria is under diagnosed because of lack of awareness and because of its insidious onset resulting in a “darkened skin” that is probably tolerated as a natural age or sun exposure related deterioration of the skin.

**CONCLUSION**

Argyria, particularly the generalized type, is worth remembering in the differential diagnosis of cutaneous pigmentation. The clinical picture and the natural course of the disease are sufficiently distinctive. The diagnosis is easily clinched by eliciting history of silver ingestion by asking leading questions (may require Sherlockian approach!) and by demonstrating silver deposition in the skin through appropriate histopathological evaluation. Failure to recognize argyria may result in prolonged psycho-social morbidity and unnecessary investigations and treatments.

**REFERENCES**


Sir,
Leukonychia is the most common dyschromia of nails. We would like to add on the information to an interesting case reported by Arsiwala[1] in your journal. In most of such nail aberrations, it is difficult to make complete diagnosis. True hereditary leukonychia may be another diagnostic possibility here. Variable expression and incomplete penetrance in total hereditary leukonychia have been documented in past.[2] Leukonychia partialis is a subtle variant or phase of leukonychia totalis with variable expression of same genetic defect.[2] Absence of family history does not necessitate diagnosis of acquired leukonychia. There have been reports documenting onset of hereditary leukonychia in childhood, not necessarily at birth.[3] Moreover, it is highly unlikely that trauma may result in total leukonychia in all finger nails simultaneously. While hereditary leukonychia is a rare condition and usually involves the entire nail, acquired type usually presents in childhood as leukonychia partialis (either punctata or transverse striae).[3] True leukonychia may occur as an isolated trait or it may be a marker of several clinical syndromes.[3]

A white appearance of nails can result from whitening of the nail plate due to alterations or dysfunctioning of nail matrix (true leukonychia); the nail bed or other underlying tissue without any matrix dysfunction (apparent leukonychia); or when nail plate alternation has an external origin, for example, in onychomycosis (pseudoleukonychia).[4,5]

Depending on the extent of each nail involved, true leukonychia may be totalis, subtotalis, or partialis (involving less than 2/3rd of nail).[4] In subtotal leukonychia, the proximal 2/3rd of the nail is white.[3] Morphologically, leukonychia partialis may again be divided into punctate, transverse, or longitudinal types.[4] Total or subtotal leukonychia is usually hereditary.[6]

Abnormal keratinization of nail plate is a possible explanation for true leukonychia. In past, biopsy of a toenail, having trauma-induced acquired leukonychia, revealed an abnormal parakeratotic strip in the lower 1/3rd of nail plate. Leukonychia occurs due to reflection of light by these parakeratotic cells and loss of nail plate transparency.[4] While hereditary true leukonychia is persistent and resistant to treatment, it requires genetic counselling to unearth other syndromes in a family. Removal or treatment of a cause in acquired leukonychia may result in complete reversal of this nail abnormality.

Since leukonychia is rarely associated with other systemic findings, one can speculate that there will be many more cases compared to anecdotal reports published sporadically. It is imperative to diagnose this rare and intriguing nail abnormality correctly because leukonychia cause extensive cosmetic embarrassment to the patient.

ACKNOWLEDGEMENT

We wish to thank the patient of total leukonychia who made us search the literature for diagnosis.

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REFERENCES

Preliminary experience of patch testing at Srinagar, Kashmir

Sir,

Allergic contact dermatitis (ACD), a delayed type of hypersensitivity reaction developing in sensitized individuals after environmental exposure to allergens, is a challenging problem with considerable morbidity and economic impact. Prevention of contact with the incriminating allergens forms the main component of management of ACD, and patch testing is a useful tool for detecting it. The exposure to allergens and the type of allergens included in standard patch test series varies considerably from area-to-area, depending on the local experience.

We conducted the study with the aim of having preliminary experience of patch testing in Kashmir, in the newly set-up contact dermatitis clinic of our department. All consecutive clinically suspected cases of ACD of all age groups visiting the clinic over a period of 7 months, from mid-May to mid-December 2012, were included in the study. Details regarding age, sex, occupation, residential background, duration and pattern of disease were recorded in case sheet after obtaining written informed consent. Personal or family history of atopy, present or past history of hypersensitivity and other dermatological and systemic illness was also recorded. Those with atopy, hypersensitive reactions were excluded in order to avoid false positive results. Cases were subjected to patch testing as per the standard guidelines, taking all necessary precautions. Patch test series used was Indian standard series (ISS), containing 25 allergens, and approved by contact and occupational dermatitis forum of India. Patch testing with conventional ISS was undertaken for convenience of getting a variety of allergens combined in a single battery. We did not select any particular occupational group or a specific patient group and so did not use any specific allergen series. Reading and grading of positivity was carried out according to International Contact Dermatitis Research Group guidelines.

Out of 85 cases patch tested, 49 were males (57.6%) and 36 females (42.4%), with age ranging from 5 years to 72 years (mean age 40.47 years ± SD 14.84), as described in Table 1. 51 (60%) cases were from urban and 34 (40%) from rural background. The duration of illness ranged from 10 days to 10 years (mean ± SD = 28.6 ± 36.20 months). Dermatitis of hands and feet was seen in 45 (52.9%) cases; non-specific pattern in 27 (37.8%), air borne contact dermatitis (ABCD) in 10 (11.8%), and photo ACD in 3 (3.5%) cases.

Out of 85 cases patch tested, 33 (38.8%), 19 males and 14 females, showed positive reactions. 20 cases showed positive reaction to one allergen and 13 to more than one, giving a total of 56 reactions. Thirty-four positive reactions were seen in males and 22 in females. Most common allergens identified were potassium dichromate and nickel sulfate showing nine reactions

---

| Table 1: Age, sex, residential distribution of cases |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Age group**   | **Males (%)**   | **Females (%)** | **Total (n=85) (%)** | **Rural (%)**   | **Urban (%)**   |
| ≤10 years       | 01              | 01              | 02              | 00              | 02              |
| 11-30 years     | 09              | 17              | 26 (30.59)      | 15              | 11              |
| 31-50 years     | 27              | 12              | 39 (45.9)       | 12              | 27              |
| 51-70 years     | 11              | 06              | 17              | 06              | 11              |
| ≥71 years       | 01              | 00              | 01              | 01              | 00              |
| **Total (n=85)**| 49 (57.6)       | 36 (42.4)       | 85 (100)        | 34 (40)         | 51 (60)         |

**Average age** 40.47 (±14.84 SD) 
**Average duration of illness** 28.6 (±36.20 SD) months
(16.1%) each. Cobalt chloride showed 6 (10.7%), thiuram mix 5 (8.9%), P-phenylenediamine (PPD) 4 (7.1%), and colophonium 4 (7.1%) reactions.

In males, the most common reactions were observed with potassium dichromate showing nine reactions (26.5%), followed by 5 (14.7%) with thiuram mix. In females, the most common allergen was nickel sulfate with nine reactions (40.9%), followed by 5 (22.7%) with cobalt chloride. Positive reaction exclusively in males was seen with potassium dichromate, PPD, mercapto mix, 2-mercaptobenzothiazole, nitrofurazone, lanolin alcohol, thiuram mix, black rubber mix, formaldehyde, and parthenolide. Positive reactions exclusive to females were due to benzocaine, nickel sulfate, and polyethylene glycol 400. No reaction was seen with petrolatum, paraben mix, gentamicin, epoxy resin, p-chloro-m-cresol, and clioquinol. Overall present relevance rate was 55.4% (31 reactions out of 56) and the results are summarized in Table 2. The occupational status of the study group and its relation with positive reaction is summarized in Table 3.

The age, sex and duration of illness variables in our study were similar to other studies.[1,2,4-7] 60% cases were from urban background, probably because our hospital is located in the main city. Dermatitis of hands and feet was the most common clinical pattern in our study, similar to some studies from India and abroad[2] and different from other Indian studies where ABCD is common.[7]

Nearly 38.8% positive reaction in our study is similar to 32.3% by Akasya-Hillenbrand et al.[6] however, differs from positive results of 63.5% by Davoudi et al.[1] 59% by Bajaj et al.[2] 63% by Handa and Jindal[7] and 64.7% by Sudhashree et al.[8] The low positive percentage tested with ISS may be because of different exposure patterns in our population than rest of the country.

The five most common allergens were potassium dichromate and nickel sulfate, followed by cobalt chloride, thiuram mix, PPD and colophonium, similar to other studies.[1,2,4-8]

### Table 2: Patch test results for each allergen of Indian standard series

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Positive results (n=56) (%)</th>
<th>Males (n=34) (%)</th>
<th>Females (n=22) (%)</th>
<th>Clinical relevance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrolatum 100%</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Potassium dichromate 0.5% pet</td>
<td>09 (16.1)</td>
<td>09 (26.5)</td>
<td>00</td>
<td>6</td>
</tr>
<tr>
<td>Neomycin sulfate 20% pet</td>
<td>02 (3.6)</td>
<td>01 (2.9)</td>
<td>01 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Cobalt (II) chloride hexahydrate 1% pet</td>
<td>06 (10.7)</td>
<td>01 (2.9)</td>
<td>05 (22.7)</td>
<td>4</td>
</tr>
<tr>
<td>Benzocaine 6% pet</td>
<td>01 (1.8)</td>
<td>00</td>
<td>01 (4.5)</td>
<td></td>
</tr>
<tr>
<td>P-phenylenediamine 1% pet</td>
<td>04 (7.1)</td>
<td>04 (11.8)</td>
<td>00</td>
<td>3</td>
</tr>
<tr>
<td>Paraben mix 16% pet</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Nickel (II) sulfate hexahydrate 5% pet</td>
<td>09 (16.1)</td>
<td>00</td>
<td>09 (40.9)</td>
<td>7</td>
</tr>
<tr>
<td>Colophonium 20% pet</td>
<td>04 (7.1)</td>
<td>02 (5.9)</td>
<td>02 (9.1)</td>
<td>1</td>
</tr>
<tr>
<td>Gentamicin sulfate 20% pet</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Mercapto mix 2% pet</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Epoxy resin 1% pet</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>2-Mercapto benzothiazole 2% pet</td>
<td>02 (3.6)</td>
<td>02 (5.9)</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Fragrance mix 2% pet</td>
<td>02 (3.6)</td>
<td>01 (2.9)</td>
<td>01 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Nitrofurazone 1% pet</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>p-chloro-m-cresol 1% pet</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Lanolin alcohol 30% pet</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Myroxylon pereirae resin 25% pet</td>
<td>02 (3.6)</td>
<td>01 (2.9)</td>
<td>01 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Thiuram mix 1% pet</td>
<td>05 (8.9)</td>
<td>05 (14.7)</td>
<td>00</td>
<td>2</td>
</tr>
<tr>
<td>Clioquinol 5% pet</td>
<td>00</td>
<td>00</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>Black rubber mix 0.6% pet</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>4-tert-Butyl phenol formaldehyde resin 1% pet</td>
<td>03 (5.4)</td>
<td>02 (5.9)</td>
<td>01 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Formaldehyde 1% aq</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Polyethylene glycol 400 100%</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Parthenolide 0.1% pet</td>
<td>01 (1.8)</td>
<td>01 (2.9)</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>34</td>
<td>22</td>
<td>31 (55.4)</td>
</tr>
</tbody>
</table>
Table 3: Positive patch test reactions to various allergens in each occupational group

<table>
<thead>
<tr>
<th>Occupational group</th>
<th>Number</th>
<th>Allergen</th>
<th>Positive reaction</th>
<th>Total reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housewives</td>
<td>21</td>
<td>Nickel</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cobalt</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colophonium</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neomycin, myroxylon, benzocaine, PEG</td>
<td>1 each</td>
<td></td>
</tr>
<tr>
<td>Service</td>
<td>21</td>
<td>PPD</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fragrance mix, thiuram</td>
<td>2 each</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myroxylon, lanolin, black rubber, potassium dichromate</td>
<td>1 each</td>
<td></td>
</tr>
<tr>
<td>Students</td>
<td>10</td>
<td>Nickel</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cobalt, PTBP</td>
<td>1 each</td>
<td></td>
</tr>
<tr>
<td>Construction workers</td>
<td>8</td>
<td>Potassium dichromate</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiuram mix, MBT</td>
<td>2 each</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colophonium, Mercapto mix, nitrofurazone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>6</td>
<td>Potassium dichromate, thiuram, formaldehyde, parthenolide</td>
<td>1 each</td>
<td>4</td>
</tr>
<tr>
<td>Cottage Industry workers</td>
<td>6</td>
<td>PTBP</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Business</td>
<td>5</td>
<td>Potassium dichromate, cobalt</td>
<td>1 each</td>
<td>2</td>
</tr>
<tr>
<td>Medical professional</td>
<td>5</td>
<td>Colophonium, neomycin</td>
<td>1 each</td>
<td>2</td>
</tr>
<tr>
<td>Unemployed</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automobile industry/driver</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>85</td>
<td></td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

PEG: Polyethylene glycol, PPD: P-phenylenediamine, PTBP: 4-tert-Butyl phenol, MBT: 2-Mercapto benzothiazole

In our study, all reactions to potassium dichromate, thiuram mix, and PPD were seen exclusively in males and all reactions to nickel sulfate and most to cobalt (5 out of 6), in females, similar to other studies.[1,2,7,8] In Kashmir, most of the construction and outdoor labor work is carried out by males and females are not involved much in outdoor work especially, construction (cement) work. So all positive reactions to potassium dichromate in our study were found in males and no female was found positive because of the above reason.

We found only one positive reaction to parthenolide than the high positive percentage seen in other Indian studies.[2,7] The positivity to parthenolide does not mean a definite implication of Parthenium weed for the ACD and does not have much sensitivity. Exposure level to Parthenium plant as such is very low in Kashmir, which could be the reason for low positivity in this preliminary study.

In conclusion, this preliminary study conducted to experience the results of patch testing at our center reveals results generally similar to that of other centers, both in country and abroad. Few differences, though, may be because of different climatic conditions, traditional, and cultural values in Kashmir causing different exposure patterns. We intend to carry forward the study in order to obtain larger data.

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REFERENCES
Syndromic management involves identifying a group of signs and symptoms in a patient and advocating treatment against the most common organism, which may be responsible. An effort to establish etiological diagnosis of the disease before instituting therapy is not required.

Vaginal discharge has been established as a syndrome. However, it fails to diagnose and treat chlamydia and gonorrhea though the two diseases may present with this manifestation. 60-70% of gonococcal and chlamydial infection are found to be asymptomatic.[1] Vaginal discharge usually visible during pregnancy or discharge seen in those on oral contraceptives is physiological, but often reported apprehending sexually transmitted disease (STD). Other women have the misconception that vaginal discharge is normal and do not report to the clinics despite suffering morbid STD. Discharge from the vagina is thus not a suitable entry point in syndromic management. Genital ulcer disease included as part of syndromic diagnosis and treatment is concerned only with the number of ulcers healed and not whether the disease is cured.[2]

Symptomatic patients do not habitually report to the STD clinics. Study among female sex workers reported only 12.7% women presenting with vaginal discharge. On examination, 51.7% were found to manifest discharge from vagina.[3] Asymptomatic patients of STD are disregarded in syndromic management. Researchers found 49% asymptomatic patients among 295 attendees in a STD clinic among responders with either genital ulcer disease or genital discharge.[4] STDs increase the spread of human immunodeficiency virus (HIV) 2-20 fold. Syndromic management fails to reduce the genital shedding of HIV and this has been demonstrated by testing genital secretions for the presence and concentrations of HIV.[5]

Overuse of antibiotics is another area of concern with syndromic management. Medicines are often prescribed unnecessarily to patients without disease.[6] Threat of antibiotic resistance looms large considering this perspective. The consistency of syndromic management has also not been validated and varies from place-to-place.

Syndromic management falls short of tackling the spiraling threat of spread of STD and with it HIV. Screening of patients, preferably laboratory based, among both high-risk and low-risk populations is the need of the hour. Behavior modification and strategies based on epidemiological data should be combined with health education. Use of mobile phones and the internet explosion can also be utilized to enhance low-cost, highly engaging and deeply permeating STD/HIV prevention and treatment support interpellations at an incomparable pace.[7] Perhaps the time has come to look closely and seriously assess aggressive strategies such as mass treatment. In comparison with syndromic management, single-round mass treatment had a greater short-term impact on HIV (36 vs. 30% over 2 years), but a smaller long-term impact (24 vs. 62% over 10 years). Mass treatment combined with improved treatment services led to a rapid and sustained fall in HIV incidence (57% over 2 years; 70% over 10 years).[8] The Piot-Fransen model of STD management depicting such mass treatment policy is based on data from underprivileged countries Uganda, Zaire, and Tanzania [Figure 1]. All consenting individuals in the reproductive age group of 15-60 years can be offered single dose of azithromycin, ciprofloxacin, and metronidazole by health-care workers visiting each household. The health-care providers must then return after a specified time period to collect biological samples from the volunteers. These results of the prevalence of sexually transmitted infections and HIV must then be compared with the projected values without such intervention. Initial high-cost of such policy may be cost effective in the long run as asymptomatic
infections are treated, contact tracing is obviated, treatment seeking behavior is not required and compliance and treatment effectiveness is assured. Antibiotic resistance may result and must be weighed against the benefits of such form of treatment. Developing countries should evaluate such an approach through meticulous trials.

A combined approach of a single round of mass treatment with syndromic management and with extensive use of the media to educate the population may be the answer to impede the burgeoning threat of association and spread of STD and HIV.

ACKNOWLEDGMENTS

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A simple and cost-effective device for mobile dermoscopy

Sir,
We had earlier presented an article mentioning the use of a simple jeweller’s loupe as a dermoscopy device.[1] Here, we present a modification by which any smart-phone camera can be converted into a dermoscopy device.

Some of the popular devices available in the market for the same purpose are Canfield...
dermscope® (Canfield scientific) and Handyscope® (FotoFinder systems Gmbh) both of which can be attached to smart-phones and serve the purpose of effective dermoscopy. These devices are especially useful in the context of e-dermoscopy or teledermoscopy, in which dermoscopic images can also be transmitted along with the clinical images for teleconsultations.[2] The main disadvantage of these devices, in the context of use in developing nations is the relatively high cost (starting from approximately 35,000INR/700USD). Moreover, most of these devices are compatible with only one particular make of smart-phones, limiting its utility.

Here, we present a simple device which can function effectively as a mobile dermoscope and can be a cheap and useful tool in mobile-phone enabled teledermoscopy.

Like in the original method,[1] we used a simple jeweler’s loupe with ×10 magnification and a built-in LED (Light-Emitting Diode) light. The loupe after extension was taped to the back of the smart-phone with the lens approximating the lens of the smart-phone camera [Figure 1]. Alcohol gel was used as the dermoscopy fluid. It should be noted that the lesions were viewed through the fluid with a small gap between the loupe and the fluid. In other words, direct contact was minimal [Figure 2].

The main advantages of this simple device are the very low cost (less than 500 INR/10dollars for the loupe) and the fact that it can be attached to any smart-phone, making it more versatile. Since both the macro images and the dermoscopic images can be taken with the same smart-phone, it becomes very easy to submit the images for teledermatology consultations. The obvious limitations are the lower quality of the dermoscopic images and the absence of polarized dermoscopy options. Further studies would be needed to validate such a tool for use for the diagnosis or triage of cases like melanoma. However, we suggest this only as a basic tool which could be an aid to mobile teledermatology especially, in rural settings and also effective in teaching students and clinicians the basics of dermoscopy, especially in the Indian context, where dermoscopy for diagnosis and triage of melanoma is not a major need.

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Figure 1: Jeweler’s loupe attached to a HTC desire HD mobile phone with cello-tape and visualization of a melanocytic nevus with the loupe

Figure 2: Melanocytic nevus over the finger (a) viewed with a jeweler’s loupe attached to a smartphone (b) and with a standard dermoscope-DERMLITE pro HR II attached to a Sony DSC W-350 camera (c)
Dermoscopic criteria for differentiating exogenous ochronosis from melasma

Sir,

There has been a sudden rise in the number of reported cases of exogenous ochronosis (EO),\(^1\)\(^-\)\(^3\) and it may not be as uncommon as previously thought. In the early stages, it is clinically difficult to distinguish EO from melasma. A worsening of pigmentation due to EO can lead to paradoxical increased application of skin lightening agents, further aggravating the condition. Thus, it is essential to distinguish early EO from melasma. The gold standard for diagnosis of EO is a skin biopsy. Dermoscopy may be an important tool to differentiate EO from melasma, and may assist in choosing the appropriate site for biopsy in suspected cases. Two cases of EO following the use of skin lightening agents for the treatment of melasma are reported and dermoscopic criteria for diagnosis are being put forward.

A 48-year-old Indian woman, Fitzpatrick’s skin type IV, presented with erythema, and gradual deterioration of her melasma. She was using sunscreens and skin lightening agents containing 2% hydroquinone in an unsupervised manner since 8 years. She noted worsening of her melasma since the past 3 years.

The second case was a 42-year-old, Indian woman, skin type IV diagnosed with melasma 14 years back. She was treated with modified Kligman’s formula containing 2% hydroquinone, 0.025% tretinoin, 1% hydrocortisone, sunscreens, and glycolic acid peels. She continued use of skin lightening agents unsupervised for 13 years, and presented with worsening of her melasma.

On clinical examination, both cases revealed grayish brown macules with interspersed “confetti like” hypo-pigmented macular areas on the malar region, a speckled pattern of pigmentation [Figure 1a-d] and a coarse texture with pinpoint, dark brown papules, which were more appreciable on palpation [Figure 1d]. In addition, case one, revealed erythema and fine telangiectasias on bilateral malar areas, whereas case two revealed mild atrophy of the malar regions and a mild bluish black hue of bilateral zygomatic regions. There was no clinical or laboratory evidence of alkaptonuria in both cases.

3 mm punch biopsies taken from the pinpoint papular lesions revealed characteristic short, stout, curvilinear, “banana-shaped,” ochre-colored fibers of varying thickness in the papillary dermis [Figure 1f]. Methylene blue staining showed dark blue staining of the ochronotic fibers [Figure 1e]. There was evidence of solar elastosis in both cases. Both cases were clinical stage II as per Dogliotti staging.\(^4\) Dermoscopic examination of both patients in areas with melasma without ochronosis revealed an accentuation of the normal pseudo-rete of the facial skin. In areas with ochronosis, greyish brown amorphous structures in the perifollicular region and some obliterating the follicular openings were observed. The pattern was curvilinear and “worm like” in some areas [Figure 2]. There was a clear demarcation between melasma and exogenous ochronosis on dermoscopy [Figure 3a-d].

EO is clinically characterized by an asymptomatic hyperchromia of the skin, usually on the sun exposed areas of the face, back, and the extensor
Figure 1: (a) Ochronosis in case 1 showing grayish brown macules with interspersed “confetti like” depigmented macular areas with erythema on the cheeks. (b) Close-up view showing speckled pattern of hyperpigmentation with a coarse texture and pinpoint, dark brown papules. (c) Bluish grey to brown macules and papules with interspersed “confetti like” depigmented macular areas. (d) Tiny pinpoint caviar like brown papules with telangiectasia. (e) Methylene blue staining showing ochronotic fibers stained dark blue. (f) Characteristic short, stout, curvilinear, “banana-shaped,” ochre-colored fibers of varying thickness in the papillary and upper dermis.

Figure 2: Dermoscopic features of ochronosis showing dark brown globules, elongated and curvilinear-worm like structures conjoined together in a reticulate pattern of ochronosis.

Figure 3: (a) Ochronosis. (b) Sharp contrast between ochronosis in the upper half and melasma in the lower half. (c) Areas of melasma without ochronosis, showed accentuation of the normal pseudo-retc pattern with a diffuse brown pigmentation. (d) Normal skin surfaces of the extremities. Tan et al.[5] recently reported variable clinical presentations of EO. Due to its varied presentation and striking similarity to melasma, especially in the early stages, clinicians require a high index of suspicion in order to make a diagnosis [Table 1]. An early diagnosis is important as
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worsening of pigmentation may lead to application of increased concentration of hydroquinone rather than terminating it immediately.

Charlin et al.\[3\] reported dermoscopic features of two patients with EO, wherein they observed blue-gray amorphous areas obliterating some follicular openings. Gil et al.\[6\] reported the dermoscopic features as irregular, brown-gray, globular, annular, and arciform structures. This was confirmed using a reflectance confocal microscope. Berman et al.\[7\] reported dark brown globules and globular-like structures on a diffuse brown background, in patients having EO, whereas those with melasma demonstrated a fine brown reticular pattern on a background of a faint light brown structure less area. Our dermoscopic findings were similar to previously reported findings. In addition, we observed a characteristic “worm-like” pattern. Thus, the dermoscopic features of EO are clearly distinct from melasma [Table 2].

Hence, dermoscopy can be employed as a rapid screening test for EO. The clinical presence of coarse texture of the skin, fine telangiectasias and hyperchromia with “speckling” or “reticulation”\[3\] should alert the clinician to resort to a dermoscopic examination, particularly in patients who are reluctant to get a facial biopsy.

To conclude, dermoscopy can be used as a rapid, non-invasive tool to detect EO, and may be a useful guide in the selection for the appropriate site for biopsy in patients with pre-existing melasma.

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LEOPARD syndrome with Wolff-Parkinson-White syndrome on electrocardiography

Sir,

LEOPARD syndrome (LS) is a rare complex of multisystemic congenital abnormalities characterized by lentigines, electrocardiographic (ECG) abnormalities, ocular hypertelorism, pulmonary valvular stenosis, abnormalities of genitalia, retardation of growth, and deafness (sensorineural). This neuro-cardio-facial-cutaneous genetic syndrome is mostly an autosomal-dominant disorder, caused by germ line missense mutation in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2, located on chromosome 12q22.\[1\]

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Table 2: Comparison of dermoscopic features of melasma and exogenous ochronosis
A 16-year-old girl, the third child of nonconsanguineous parents, presented to us with numerous tiny hyperpigmented spots scattered over face, trunk, and limbs, admixed with multiple, bigger, hyperpigmented flat discrete lesions. They started appearing at the age of 6 and have been progressively increasing in number since then but have always remained asymptomatic and nonremitting. She also gave history of chest deformity since birth, but denied history of any syncopal attacks, dyspnea, and cyanosis. There was no history of deafness, abnormalities of genitalia, or secondary sexual characteristics. Her deceased father had similar cutaneous lesions all over his trunk and had died a sudden death at the age of 42, due to an unknown cause. No one else in the family, including her two siblings, is similarly affected.

On general examination, she was stunted for age, with a height of 100 cm (below 95th percentile for her age) and had significant scoliotic deformity of thoracic spines with winging of scapula and mild pectus excavatum. She also had ocular telorism with a broad nasal root [Figure 1]. Clinically, cardiac examination was unremarkable, but electrocardiogram showed left axis deviation, shortened PR interval (106 ms), widened QRS interval (130 ms), with a slurred upstroke (delta wave) suggestive of Wolff-Parkinson-White (WPW) syndrome, which is an anomalous accessory connection between atria and ventricles which results in acceleration of passage of impulse from atria to ventricle[2] [Figure 2]. Echocardiography showed no structural or functional abnormalities. Visual and auditory brainstem response testing was normal. Her routine biochemical parameters, coagulation profile, and hormonal profile were all within the usual limits. Ultrasound study showed normal genitourinary system.

On cutaneous examination, the girl had numerous lentigines with scattered distribution over face, chest, back, axillae, abdomen and thighs, admixed with multiple discrete hyperpigmented café-au-lait macules. Histopathological examination of the suspected lentigines showed an increased number of melanocytes with regular distribution of melanin in the basal layer with elongation of rete ridges into the dermis, confirming the diagnosis of lentigen simplex.

According to criteria proposed by Voron et al., to diagnose LS, the patient must have lentiginosis along with at least two of the minor criteria, which are cardiac structural or ECG abnormalities, genitourinary abnormalities, endocrinial abnormalities, neurologic defects, cephalofacial dysmorphism, shortness of stature, skeletal abnormalities, and other cutaneous abnormalities. If lentigines are absent, three other clinical features must be present.[3] LS is characterized by highly variable phenotypic expressivity [Table 1]. Other syndromes with lentigines that need to be differentiated from LS are Cronkhite-Canada syndrome, Carney complex and Bandler syndrome. Noonan syndrome is another syndrome that shares many features with LS and careful differentiation between the two syndromes is important, because distinct mutations in the same PTPN11 gene has also been attributed for Noonan syndrome which usually present with typical facial dysmorphism and clinical features like short-webbed neck, cryptorchidism in

![Figure 1: (a) A 16-year-old girl with lentiginosis on face and neck with multiple café-au-lait macules. (b) Same girl with a broad nasal root and hypertelorism. (c) Shows scoliosis of thoracic and lumbar spines in the same patient](image)

![Figure 2: Electrocardiogram showing left axis deviation, shortened PR interval (106 ms), widened QRS interval (130 ms) with a slurred upstroke (delta wave) suggestive of Wolff-Parkinson-White Syndrome, with nonspecific ST-T changes in the anteroseptal and inferior leads](image)
The incidence of WPW syndrome has been described as premature ventricular contractions, paroxysmal atrial tachycardia, shortened PR interval among others.[6]

In general, the long-term prognosis of the LS patient is favorable, but patients with cardiac abnormalities need periodic assessment because, despite cardiac involvement, most patients of LS remain asymptomatic. According to some authors, LS patients have increased melanocytic activity, secondary to an abnormal development of neural crest cells and increased β-adrenergic effector activity in the myocardium.[8]

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Recurrent lymphocytic Sweet’s syndrome

Sir,
Sweet’s syndrome (SS), also known as acute febrile neutrophilic dermatosis or Gomm-Button disease is characterized by fever; acute onset of painful, erythematous or plum-colored papules, plaques or nodules; peripheral neutrophil leukocytosis; and a dense neutrophilic infiltrate on histology, according to the classical description.[1] But rare histological presentations with lymphocytic and histiocytic infiltrate in patients with myelodysplasia have been reported.[2]

Here, we report a case of recurrent skin eruption resembling SS associated with dermal lymphocytic infiltrate without underlying hematological abnormality.

A 40-year-old female presented with recurrent episodes of red raised tender lesions over face, neck, forearms, and upper back of trunk of 8 years duration. Each episode was associated with high grade and continuous fever. There was no history of malar rash or arthralgia or photosensitivity. Each time she was treated with systemic corticosteroids, lesions responded completely, but recurred after a symptom free interval of 6-9 months.

Cutaneous examination revealed multiple plum-colored and erythematous edematous tender plaques of size ranging from 1 × 1.5 to 3 × 4 cm size over face, neck, upper chest, upper back, and bilateral forearms with some lesions showing pseudovesiculation [Figures 1 and 2]. No mucosal lesions were present. Systemic examination was within normal limits. The pathergy test was positive. Hematological examination showed leukocytosis with neutrophilia and raised erythrocyte sedimentation rate (ESR). Peripheral smear examination showed neutrophilia with toxic granules. Liver and renal function tests were normal. Antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), and cytoplasmic-ANCA (c-ANCA) were negative; antistreptolysin O (ASO) titer was within normal range. Skin biopsies were taken during each episodes of exacerbation (a total of five biopsies during 8 years of disease course) and review of all slides consistently showed dense lymphocytic infiltrate in the dermis [Figure 3a and b], with few areas of perivascular pattern and no basal cell degeneration. Immunohistochemistry showed CD3 +ve [Figure 3c], CD20 −ve cells confirming T cell lineage with no other or atypical cells. Direct immunofluorescence (DIF) did not reveal any complement or immunoglobulin deposits in the vessels or dermoepidermal junction. Bone marrow aspiration studies done repeatedly were of normal cytology.

Chest radiogram, ultrasonographic studies of abdomen and pelvis, and neurological evaluation were unremarkable. A detailed literature search was made, and based on the aforementioned findings a diagnosis of recurrent lymphocyte predominant SS was made and the present episode was managed with systemic steroids. The lesions completely subsided and she is presently under follow-up.

Dr. Robert Douglas Sweet first described this entity in eight women with a “distinctive and fairly severe illness” in 1964.[3] The name Gomm-Button disease referred to the initial two patients with this condition.[1] Histopathological description of SS is a diffuse dermal infiltrate of mature neutrophils. Several studies suggest that there may be an admixture of lymphocytes and/or eosinophils, either of which can be prominent in some cases.[1]

A unique clinicopathologic subset of nine SS patients has recently been recognized where clinically diagnosed SS skin lesions showed an initial lymphocytic infiltrate in the dermis (initial SS) and late neutrophilic infiltrate (late SS) after 24-96 months. All these patients developed myelodysplastic syndrome later on.[2] Literature search revealed similar reports of lymphocytic infiltrate occurring 2 months to 4 years prior to classical neutrophilic infiltrate.[4-6]
‘Histiocytoid SS’ is a recently described histological variant of SS with infiltration of histiocyte-like cells into the upper dermis. These cells are considered as immature myeloid cells from the bone marrow in early acute stage.[7]

In our case, the clinical presentation during each episode was typical of SS, but with dense dermal lymphocytic infiltrate. The possibilities of Jessner’s lymphocytic infiltrate (JLI), polymorphic light eruption (PMLE), and lupus erythematosus (LE) were ruled out with the characteristic clinical appearance, presence of fever, absence of basal cell degeneration in biopsy, and negative DIF. The bone marrow cytology was normal repeatedly. Unlike the previous reports, in our case there was no evidence of myelodysplasia or hematological malignancy or other systemic illnesses even after detailed evaluation and the dermal infiltrate has remained lymphocytic for 8 years. The presence of neutrophils in the dermis might herald an underlying malignant transformation and persistence of lymphocytes for years point to a benign nature of disease.

We propose that there can be an atypical lymphocytic SS with typical clinical features which may recur, not associated with myelodysplasia or hematological malignancy and need to be considered as a distinct entity. No report of such a rare presentation is available from India.

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Letters to the Editor


Functional esthetic rehabilitation of a 7-year-female patient with hereditary ectodermal dysplasia using flexible denture

Sir,

Hypohidrotic ectodermal dysplasia (HED) is a congenital syndrome characterized by sparse hair, oligodontia and reduced sweating.[1] It is caused by mutation in the ectodysplasin A gene, which is inherited as X linked recessive pattern. However, less commonly HED is also caused by mutation in ectodysplasin-A receptor or EDARADD gene, which has an autosomal dominant or autosomal recessive pattern of inheritance.[2,3] Expression of symptoms are fully blown in affected males, but females are usually carrier.[2,3] Dental manifestations include conical or pegged shaped teeth, hypodontia or complete anodontia, delayed eruption of permanent teeth, thin alveolus ridge and dry oral mucous membrane.[1]

Children with HED have problems with mastication, speech, esthetic and psychology: Affecting their quality of life.[1] To restore the lost functions and to improve self-confidence removable partial denture, complete denture, implant supported complete denture and over denture can be given.[3] We hereby, describe the oral management of a female child with HED using the flexible over denture.

A 7-year-old girl with HED reported with the complaint of inability to masticate, unesthetic appearance and teasing from her peer group. Patient gave a history of decreased sweating, dry oral mucosa and skin and raised body temperature. She was born of a normal delivery and her psychomotor development was normal. Patient’s family history revealed that the mother’s cousin brothers had similar problems. Intra-oral examination revealed dry oral mucosa, conical shaped teeth, oligodontia and thin alveolar ridges [Figure 1]. Extra-oral examination showed sparse hair, frontal bossing, depressed nasal bridge, sunken cheeks and everted lips [Figure 1]. Nails appeared normal. Systemic examinations were within the normal limit. Based on history and clinical examination a diagnosis of HED was made.

At the age of 7 years, skeletal maturity is incomplete hence flexible removable over dentures were given to reestablish occlusion, mastication, speech and esthetic [Figure 2]. Primary impressions of both jaws were made with irreversible hydrocolloid impression material. Custom trays were prepared and border molding was carried out with a heavy body polyvinyl siloxane material. The final impressions were made with medium and light body type of rubber base impression material. Maxillo-mandibular relation was recorded and teeth were arranged according to a balanced occlusal scheme. Maxillary and mandibular prostheses were fabricated in Valplast resin by injection molding technique. Prior to insertion, the valplast partial denture was immersed for a minute in warm water. The heat exposure assures a very smooth initial insertion and allows the denture to adapt to the underlying tissue. The dentures were then inserted in patient’s mouth [Figure 2]. Patient was educated about proper insertion, removal and hygiene of the over denture. Future visits were scheduled for 6 months to monitor bone growth and for denture relining.

Oral care: As there are many oral manifestations, there is no standard formula for dental treatment. Treatment needs may include: Preventive measures against caries, restorations of decayed teeth, partial dentures, over dentures, implant supported denture and timely orthodontic care. In the present case, the child was given flexible removable partial denture.
The advantage of flexible partial denture: Improved esthetic, exceptionally strong and flexible, good biocompatibility, free from an allergic reaction, does not irritate the oral mucosa and satisfy daily diet for the child.[4] Implant supported complete denture is avoided until adolescence because of increased risk of implant failure due to insufficient alveolar bone support. Secondly, there is a risk of trauma to tooth germs and interferences in craniofacial growth.[5]

Orthodontic care is one of the major concerns of families with children affected with HED. Because early orthodontic care in such children not only improves alignment of permanent teeth, but also improves facial profile and prevent psychological trauma associated with this condition. Orthodontic treatment using flexible dentures can enhance growth process, maintain favorable maxillomandibular relations and provide a permanent base for prosthetic rehabilitation. This type of combination treatment ultimately benefits stomatognathic function, vertical growth and enhance the facial appearance and profile. In a recent case, authors have incorporated midline jackscrew in removing partial denture to enhance transverse growth and closure of midline diastema.[6] However, combine delivery of orthodontic and prosthetic treatment can lead to design compromise leading to compromised functional stability. Therefore, such patients require close attention and require frequent replacement of prosthesis.

Individuals are advised to take frequent sip of water through the day.

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Cutaneous metastasis of an advanced prostate cancer

Sir,

Primary visceral malignancies uncommonly present with skin involvement with a reported incidence between 2% and 9% and their presence is indicative of an advanced disease and poor prognosis. The most common tumors to metastasize to skin are breast, lung, colorectal, renal and ovarian carcinomas. Despite the high incidence of prostatic cancer, cutaneous and subcutaneous metastases of this cancer are extremely rare, seen in <1% cases. We report a case of an elderly male with carcinoma of the prostate with multiple cutaneous metastases.

A 70-year-old man presented with 1 month history of multiple skin colored to erythematous papulonodular lesions variable in size over the pubic region and inner aspects of thigh. These lesions first appeared over the suprapubic area and progressively increased in size and involved inner aspects of thighs and left inguinal region. These lesions were associated with discomfort, but were not associated with ulceration and bleeding. About a year back, he had presented to the emergency department with urinary retention. He was diagnosed to have carcinoma of the prostate and his prostate-specific antigen (PSA) level was found to be 210 ng/ml.

Transrectal ultrasound guided biopsy was carried out, which revealed poorly differentiated prostatic adenocarcinoma with a Gleason score of 9 in all the 8 core biopsies performed. There was no perineural invasion or extraglandular extension. A staging bone scan was performed at the time of diagnosis, which did not show any evidence of bony involvement.

Patient underwent a complete androgen blockade with Buserelin and Cyproterone acetate. Almost 1 year after the diagnosis, patient noted development of cutaneous lesions at the pubic region. These lesions were considered to be cutaneous metastases from the prostatic cancer. Patient also complained of multiple bone pains, loss of weight and appetite. Repeat bone scan revealed multiple metastatic lesions of pelvic bones.

Cutaneous examination revealed multiple erythematous dome shaped papulonodular lesions, with a smooth shiny surface, varying in size from 5 mm to 1 cm presenting over the suprapubic region, left inguinal region and inner aspect of left thigh [Figure 1]. These lesions were non-tender, firm in consistency and fixed to the overlying skin, but not to the underlying structures. Scrotum was normal, but penis was thick, edematous infiltrated and deformed in shape. Rest of the mucocutaneous examination was unremarkable. Systemic examination of the patient was also normal.

Routine investigations showed a hemoglobin of 7.8 g/dl and increased liver enzymes (serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase). Fine needle aspiration cytology revealed adenocarcinomatous cells of uncertain origin. Excisional biopsy of one of the papules revealed stratified squamous epidermis on the surface, with rows and prostate acini-like glandular structures appearing due to the ectatic lymphatic spaces due to the lymphangiectasia secondary to metastasis blocking lymphatics [Figure 2]. PSA level was also elevated.

Radiographs of pelvis revealed diffuse osteosclerotic lesions. Chest radiograph as well as ultrasound abdomen were normal. Patient was subjected to palliative care with radiotherapy to the pelvic bones.

Cutaneous metastases from internal malignancies are relatively rare, seen in about 2-9% of malignancies. Cutaneous metastases occur more commonly with mammary, pulmonary, renal and colonic cancers and are seen in the advanced stage of malignancy, associated with a poor prognosis. Although carcinoma of the prostate is common, it is responsible for lesser than 1% of cutaneous metastases.

Cutaneous metastases from prostatic carcinoma are usually asymptomatic and may occur at single or multiple sites. The most common sites involved are the lower abdomen, genitalia and thighs. Metastatic lesions are usually papules and nodules and they rarely ulcerate. They may have a zosteriform distribution or may appear as sclerodermoid lesions. Other rare manifestations include priapism, penile metastasis, gynecomastia and breast metastasis. Skin metastases from prostatic cancer are an ominous finding and most of the patients die within 6 months.

Although the mechanism of cutaneous involvement is not well-understood, suggested routes include embolization of vessels, dissemination through lymphatics and through perineural lymphatics.
Immunohistochemistry is an important tool in establishing organ of origin when histology is not conclusive. A large majority of metastatic adenocarcinomas are P501S positive (99%). A small subset of metastatic prostatic adenocarcinoma shows significant differences in staining intensity and extent of PSA and P501S and therefore combined use of these markers may result in increased sensitivity for detecting prostatic origin. Cutaneous metastases from a prostatic carcinoma signifies an advanced stage, aggressive behavior and a grave prognosis, with disease specific survival lesser than 6 months. Thus, the treatment at this stage is palliative care, which includes keeping the lesions dry and clean. Debridement is a good option for bleeding or crusting lesions.

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REFERENCES


Psoriatic plaques with leukotrichia: A novel observation

Sir,

Hair is an important skin appendage as changes in hair color, volume and texture may be an indicator to many dermatological conditions. The myriad of hair colors include shades of grey, yellow, brown, red and black, produced by combinations of two primary pigments, eumelanin and pheomelanin, in varying proportions. These pigments are derived from melanocytes of the upper root of the hair bulb, which imparts color to the hair cortex during the anagen phase of the hair cycle.

The population density of melanocytes in the hair bulb is much greater than in the epidermis (approximately one melanocyte to four basal keratinocytes in the
upper hair bulb compared with a ratio of 1:25 in the basal layer of the epidermis.\textsuperscript{[1]} Leukotrichia, meaning “white hair”, is caused by a variety of genetic and acquired disorders culminating in the loss of these hair bulb melanocytes. The dermatological conditions usually associated with leukotrichia include vitiligo, alopecia areata, Vogt-Koyanagi-Harada syndrome, Alzegandrin syndrome, Piebaldism, Waardenburg syndrome, Tuberous sclerosis etc.\textsuperscript{[1]} However, leukotrichia has never been reported on psoriatic plaques unless as a part of co-localized vitiligo.

We present a case of 45-year-old, HIV negative male with generalized stable plaque psoriasis.

The patient presented in dermatology OPD with history of red, raised, scaly lesions all over the body for the last 15 years. He reported that the hair over the lesions was initially black but five years ago, turned white rapidly over a span of three months. On examination, well demarcated, variable sized, erythematous, raised, indurated scaly plaques with leukotrichia strictly restricted to the plaques were present over the extremities. Hairs elsewhere were black [Figure 1]. Grattage test and Auspitz sign were positive. Skin biopsy revealed hyperkeratosis, parakeratosis, suprapapillary thinning and elongation of rete ridges, which favored the clinical diagnosis of psoriasis [Figure 2a]. Staining with HMB (Human melanin black) - 45 revealed scattered melanocytes in the basal layer of the epidermis [Figure 2b and c]; this ruled out co-localized vitiligo. Melanocytes were conspicuously absent from the hair follicles [Figure 2c and d]. Methotrexate was started after routine hematological and biochemical investigations, following which the psoriatic plaques improved but the hair color remained unchanged.

Psoriasis is a chronic, recurrent, T cell mediated disorder of keratinization; characterized by red, scaly, sharply demarcated, indurated plaques particularly affecting the extensors. The underlying mechanism is still debatable; though most of the recent literature points to an immune mediated mechanism, implicating Th17-type helper T cell.\textsuperscript{[2]}

Several studies and case reports have documented the coexistence and co-localization of psoriasis and vitiligo.\textsuperscript{[3]} Koebner’s phenomenon is common to both the disorders.

Increased level of tumor necrosis factor alpha (TNF-\(\alpha\)) has been demonstrated in both psoriatic plaques and perilesional skin of vitiligo patients. Even if we try to explain the presence of white hair over the psoriatic plaques through a similar mechanism, the selective destruction of follicular melanocytes with sparing of epidermal melanocytes poses a mystery which is hard to solve. The fact, that ‘follicular-melanin unit’ resides in the immune privileged proximal anagen hair bulb,\textsuperscript{[4]} makes this observation even more intriguing. Selective loss of follicular melanocytes without concomitant destruction of epidermal melanocytes has only been noticed in acute alopecia areata in which the inflammation is concentrated in and around the bulbar region of anagen hair follicles.\textsuperscript{[5]}

Follicular pigmentation is governed by numerous intrinsic factors.
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and extrinsic factors including hair cycle-dependent changes, racial and gender differences, environmental influences, genetic defects and age-associated changes. Recently, there has been tremendous research to elucidate mechanisms of age related selective destruction of follicular melanocytes, evidenced by graying of hair with sparing of epidermal melanocytes. It has been observed that the follicular-melanin unit of greying hair is associated with increased melanocyte apoptosis and oxidative stress, which could be the result of impaired antioxidant mechanisms. A similar free radical injury can possibly explain our finding of white hair in the psoriatic plaques, since psoriasis is an inflammatory disorder with increased cell turnover. However, the fact that this observation has never been reported previously in psoriasis, which is a relatively common disease, remains an enigma.

Thus, this case is unique as the current knowledge of the pathogenesis of psoriasis fails to explain leukotrichia restricted to psoriatic plaques. Whether this novel finding signifies any change in prognosis or course of the disease in the relevant patient can only be explained with advanced molecular and further observational studies.

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Cutaneous T-cell non Hodgkin lymphoma in a patient with idiopathic CD4+ lymphocytopenia

Sir,

Idiopathic CD4+ lymphocytopenia (ICL) is a rare heterogenous condition, often detected in middle age, following the occurrence of an opportunistic infection in a person without known immunodeficiency or immunosuppression. Here we report, a patient with ICL who presented with recurrent furuncles and who subsequently developed cutaneous T-cell non-Hodgkin lymphoma (T-cell NHL).

A 33-year-old man attended the out-patient-department of our hospital with an 8 month history of recurrent furuncles distributed over scalp, lower limbs, and back of trunk. His past medical history was insignificant and he was not on any drugs. Swab culture from furuncles confirmed staphylococcal infection.

A detailed evaluation for any underlying immunosuppression including a complete hemogram, liver, and renal function tests, random blood sugar, serum immunoglobulins, chest X-ray, and peripheral smear were within normal limits. Serology for p24 antigen, HIV 1 and 2 and human T cell leukemia virus (HTLV) 1 and 2 antibodies, venereal disease research laboratory (VDRL) test, hepatitis B antigen (HBsAg), Anti HCV (hepatitis C virus) antibody and antinuclear antibody were also negative. A low CD4+ T-cell count of 186 cells/mm³ was the only abnormal finding. This can be a transient, non-specific observation in an infection and he was treated with appropriate antibiotics.

Patient was re-evaluated after 3 months and his skin lesions had all subsided, but the CD4 count was still low at 180 cells/mm³. A repeat clinical and
laboratory work up failed to detect any cause for the persistent lymphocytopenia. Hence, we arrived at the final diagnosis of ICL. As the cluster of differentiation (CD) 4 count was below 200, he was prescribed cotrimoxazole prophylaxis and was urged to be under regular follow-up.

He returned 1 year later with pruritic, infiltrated papules, and plaques all over the body and significantly enlarged cervical, axillary, and inguinal lymph nodes [Figure 1a]. CD4 count was 178 cells/mm³. Again there was no evidence of retroviral infection. Ultrasound abdomen revealed hepatosplenomegaly and retroperitoneal lymphadenopathy. Biopsy from an enlarged cervical node showed loss of normal architecture with moderate to marked infiltrate of atypical lymphocytes. Histology [Figure 1b] of the skin lesions revealed dermal infiltrate of atypical lymphocytes without epidermotropism. On immunohistochemistry, the tumour cells were CD3 +ve [Figure 2a], CD4 +ve [Figure 2b], CD8 +ve [Figure 2c] and CD20–ve [Figure 2d] pointing to a diagnosis of cutaneous T-cell NHL. The patient was referred to Hemato-Oncology Department, chemotherapy was initiated, but while on chemotherapy he developed septicemia and succumbed to death.

CDC defined ICL in 1992 as (1) CD4+ T-lymphocyte level <300 cells/mm³ or <20% of total lymphocytes, at a minimum of two separate time points, at least 6 weeks apart. (2) No serological evidence of HIV infection. (3) Absence of any defined immunodeficiency or therapy that can depress CD4 count.

Various theories put forth to explain the etiology of ICL include diminished production of T cell precursors, accelerated T-cell apoptosis, biochemical failure of the CD3-T' cell receptor pathway, defective generation of tumour necrosis factor (TNF)-α and interferon (IFN)-γ and antibodies against CD4+ T cells. Clinical picture varies from an asymptomatic laboratory abnormality to life threatening complications such as opportunistic infections and neoplasms. It is documented in one series that, in about one fifth of patients, lymphocytopenia resolved within 3 years of diagnosis whereas in the majority, most serious complications developed during the first 2 years of diagnosis.

Our patient manifested T-cell NHL 1 year after the confirmation of ICL.

Previous reports point to a predominance of Burkitt’s and other B-cell lymphomas in ICL, but our patient developed T-cell NHL, which is a rare occurrence. A T-cell lymphoma in the setting of CD4+ lymphocytopenia is hard to explain. A pathogen specific, immune response driven, CD4+ T-cell activation and turn-over is proposed to be the root cause of lymphocytopenia in ICL. This constant activation may precipitate the monoclonal expansion of atypical cells in the remaining T-cell population. On searching the literature, we came across only one more instance of T-cell neoplasm in ICL and this was reported by Moradi et al. (angiocentric nasal T-cell lymphoma) in a 13-year-old boy.

Current recommendations (including cotrimoxazole...
Letters to the Editor

prophylaxis) for the treatment of ICL are based mainly on the experience with HIV patients.[1] IFN-γ has been tried to boost the depressed CD4 levels.[3]

We report this case to stress the need to consider ICL, in any patient (with no known immunodeficiency) presenting with opportunistic infections. Had it not been diagnosed earlier, lymphocytopenia in our patient would have been attributed to the lymphoma. Meticulous documentation and analysis of the clinical features and disease progression in those affected, may help us to improve the diagnostic definition and treatment options for this rare condition.

ACKNOWLEDGMENTS

We express our sincere gratitude to Dr. Sunitha Balakrishnan, Asst. Professor, Department of Pathology for the help in analysing the histopathology specimens.

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A case of linear immunoglobulin A disease with dapsone hypersensitivity and its management strategies

Sir,

Linear immunoglobulin A (IgA) disease is a rare acquired autoimmune subepidermal vesiculobullous disorder with an estimated prevalence of 0.5 per 1,000,000 adults.[1] Drugs and infections have been reported to be associated.[2] We herein report a patient of severe linear IgA disease with unusual therapeutic challenges.

A 27-year-old lady presented with fever of 7 days duration, followed 2 days later by multiple painful fluid-filled lesions over body. Dermatological examination revealed multiple polysized, discrete to confluent crusted plaques with vesicles along margins in generalized distribution (cluster of jewel appearance) [Figure 1]. Multiple hypopigmented macules and pustules were also present. Bulla spread and Nikolsky’s signs were negative. There was no mucosal involvement. Clinical differential diagnosis of subcorneal pustular dermatosis, linear IgA disease, and bullous pemphigoid was offered.

Initial skin biopsy revealed subepidermal bulla with a neutrophilic infiltrate in the dermis [Figure 2]. Direct immunofluorescence showed deposition of IgA linearly along basement membrane. Patient was diagnosed as a case of linear IgA disease and was started on oral dapsone 100 mg once daily. The lesions showed gradual resolution over 4 weeks.

However after 4 weeks, patient reported back with fever and extensive redness and scaling over body. On examination, patient was febrile, had icterus, and an extensive erythematous maculopapular rash. Investigations revealed serum bilirubin of 3.3 mg/dL, alanine aminotransferase levels of 162 IU/L, and aspartate aminotransferase levels of 92 IU/L with absolute eosinophil count of 1383 cells/cm. Ultrasound abdomen revealed hepatosplenomegaly. Patient was diagnosed to have dapsone-induced hypersensitivity syndrome and dapsone was stopped. Patient was started on oral prednisolone 60 mg and colchicine 0.5 mg thrice daily.

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In spite of this therapy, after 7 days, the bullous lesions relapsed and serum bilirubin levels began to rise. With two different problems of linear IgA dermatosis and dapsone hypersensitivity syndrome, intravenous pulse methylprednisolone 1 g for 3 consecutive days was administered. The patient started improving on the 2nd day of pulse therapy. She was restarted on oral prednisolone 60 mg after completion of the pulse therapy and colchicine was continued.

Two weeks later, patient developed multiple furuncles over the extremities. There was no evidence of any immunosuppression in the form of diabetes, human immunodeficiency virus infection, or any other associated disorders. The patient was started on oral linezolid 600 mg twice daily, prednisolone was tapered by 10 mg every 2 weeks, and colchicine was continued. The furuncles regressed in duration of one week. When tapering of oral prednisolone had reached 20 mg after 4 weeks, patient again started developing multiple fluid-filled lesions over extremities similar to the initial episode. Repeat skin biopsy and direct immunofluorescence showed typical features of linear IgA dermatoses and patient was restarted on full dose of prednisolone 60 mg and colchicine was stopped. The skin lesions gradually started resolving and liver function tests also became normal after 8 weeks. The steroids were continued with progressively tapering doses for a total duration of further 12 weeks after which all the skin lesions resolved, not leaving any trace of pigmentation or scars. The patient has presently been followed-up for 6 months during which she has had no recurrence.

The clinical presentation of linear IgA disease can be heterogeneous and can mimic other blistering diseases such as dermatitis herpetiformis, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa acquisita, and also other groups of disorders like erythema multiforme, toxic epidermal necrolysis, systemic lupus erythematosus, and erythema annulare centrifugum. Linear IgA disease is a chronic relapsing condition with mild cutaneous manifestations usually. Our patient had very severe cutaneous involvement without mucosal involvement which is not seen very commonly.

Dapsone is the most effective drug in managing this condition with excellent initial responses and long-term remissions being reported. Colchicine, thalidomide, cyclosporine, niacinamide, antibiotics like sulfonamides and amoxicillin are also reported to be effective. Oral steroids have been combined with dapsone for better results in recalcitrant cases. However, use of pulsed steroids in heavy intravenous doses has not been described previously. Dapsone hypersensitivity syndrome being concomitantly managed with severe linear IgA disease is another therapeutic challenge not faced very often.

Herein, we had a patient of severe cutaneous linear IgA disease who had various therapeutic challenges in the form of dapsone hypersensitivity syndrome and nonresponse to colchicine. She was in the reproductive age group and hence thalidomide was contraindicated. Corticosteroids seemed to be the only panacea whenever she got into trouble and even pulsed steroids had to be given. Such unusual therapeutic requirements in a case of linear IgA disease have rarely been mentioned in literature.
Letters to the Editor

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INTRODUCTION

Adverse drug reaction is a noxious and unintended response to a drug at normal doses used in humans for prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function (WHO).\(^1\) Cutaneous adverse drug reactions are a frequent problem in clinical practice and comprise 1-2% of outdoor and 5-10% of indoor patients in dermatology practice.\(^2\) It is often difficult to pinpoint the offending drug from temporal correlation/history alone as most affected patients are on multiple medications, and the clinical picture is often not diagnostic. Although, re-challenge/provocation tests, intradermal tests or skin prick tests are of significant value in identifying the culprit drug, they are time consuming, need expertise or may even re-precipitate life-threatening adverse drug reaction that may raise ethical issues. Availability of basophil degranulation/lymphocyte activation tests remains limited, has low sensitivity/specificity and may even be negative during acute stage of drug hypersensitivity. Radioallergosorbent test for drug specific IgE, histamine release test, and passive hemagglutination test with sensitivity/specificity nearly similar to skin tests have limited availability/applicability in routine clinical practice. An increased focus has been witnessed in recent years on the utility of drug patch test in cutaneous adverse drug reactions since it is easy to perform, relatively safe, and the only in-vivo challenge test available. Hence, it becomes imperative to revisit methodology, interpretation, and clinical relevance of drug patch testing.

MECHANISMS OF ADVERSE DRUG REACTIONS

It will be prudent here to recapitulate briefly the mechanisms involved in adverse drug reactions. The majority (nearly 95%) of adverse drug reactions are Type A (augmented) reactions which are dose-dependent and predictable from the primary and secondary drug pharmacology while Type B (Bizarre) reactions are idiosyncratic, unpredictable from drug pharmacology, and determined by patient-specific susceptibility factors.\(^3\) They can be “non-immune mediated (drug intolerance)” due to inadequate or imperfect metabolic detoxification leading to hemolysis, bone marrow toxicity or neurotoxicity from toxic metabolites or “pseudo-allergic” due to histamine, leukotrienes, or other mediators released from direct basophil/mast cell de-granulation. These are often difficult to distinguish from true immunologically mediated immediate type allergic responses (e.g., asthma, anaphylaxis, and urticaria/angioedema-like reactions due to drugs like opiates, muscle relaxants or radio contrast media). Table 1 lists four main classes of immune effector mechanisms involved in immune mediated Type B (immunologic) reactions which are relevant for drug patch testing.\(^3\)

BASIC PRINCIPLES, METHODOLOGY, AND REPORTING OF RESULTS

The basic principles and methodology for drug patch test remains same as that in patch testing for contact
dermatitis. The T-cells get activated by adaptive immune mechanism from hapten-antigen presenting cells (APCs) and human leukocyte antigen (HLA) complex (HLA-class I and/or II). For this, drug molecule or the metabolite becomes a hapten that binds with protein to form an antigen which then is processed by APCs. Once T-helper cells get activated, they proliferate to produce clones of memory/effector T-cells with specificity for that immunogen with ability to activate immune effector mechanism (immunological memory) or they in turn help B cells to produce antibodies (IgA, IgG, IgE). It requires 7-10 days to develop immunological memory (sensitization phase) meaning thereby that one must have continuous exposure for this much period to the offending drug for tissue damaging hypersensitivity to develop (elicitation phase). Re-exposure to the culprit drug will elicit similar clinical reaction pattern in previously sensitized individuals. This is the background principle for drug patch testing.

Finn chamber method is used for drug patch testing and test units are applied over non-hairy, upper back after cleansing with ethanol without rubbing [Figure 1]. For drug reactions such as fixed drug eruptions (FDE), Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN), intertriginous/flexural exanthem less affected skin sites may remain negative while, initially affected skin sites elicit more positive responses and should be selected for patch testing.[4,5] The patient is instructed to leave the patches in place for next 48 h (2 days), avoid rubbing, scratching, or wetting them. Patches are removed and marked clearly and responses are read 1-2 h after letting the skin regain its normal contour and the non-specific skin irritation subsides. Patch test results can be negative on day 2 (D2) but, positive when read on day 4 (D4). Readings should be made at 20 min for urticaria or anaphylaxis-like immediate adverse drug reactions from betalactam antibiotics, neomycin, gentamycin, bacitracin, diclofenac. For drug photo-patch test, performed in drug induced photodermatitis, photo allergic/toxic reactions, two sets of patch tests are applied. One set of drug photo-patch test is irradiated with ultraviolet (UV)-A (5 or 10 J/cm²) at 24 or 48 h (D1 or D2).[6] It will be pertinent to mention here that the protocol for reading of patch test results in cases of FDE is not different.[7] For obvious reasons treatment with systemic corticosteroids or immunosuppressive drugs is required to be stopped at least 1 month before patch testing.[6] Similarly, topical corticosteroids should not be used over test sites for at least 2 weeks.

Table 1: Type B (immunologic) reactions

<table>
<thead>
<tr>
<th>Type of hypersensitivity</th>
<th>Immune effector mechanism</th>
<th>Clinical manifestation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (immediate or anaphylactic)</td>
<td>IgE bound to surface of mast cells or basophils. antigen (Ag) binding causes mast cell degranulation, release of histamine and other mediators</td>
<td>Urticaria/angioedema, asthma, anaphylaxis</td>
<td>Skin/prick test and intradermal test (with 15-min response) will detect it except in pseudo-allergic types</td>
</tr>
<tr>
<td>Type 2 (cytotoxic)</td>
<td>Antibodies (Abs) to Ag determinants on cell surface are target for IgG/IgM Abs. Cells/ tissues damaged by activated complement or by binding to cells through Fc receptors, and activate cytotoxic killing, e.g., by K cells</td>
<td>Pemphigus, neutropenia, thrombocytopenia, hemolysis</td>
<td>Skin manifestation is rare and mainly as pemphigus</td>
</tr>
<tr>
<td>Type 3 (immune complex)</td>
<td>Circulating immune complex deposited in vascular beds or on tissue surfaces, complement is activated, neutrophils attracted and their products damage tissues</td>
<td>Hypersensitivity vasculitis, Henoch-Schonlein purpura</td>
<td>Skin tests are of no value</td>
</tr>
<tr>
<td>Type 4 (delayed type)</td>
<td>T-lymphocytes (CD4 or CD8) producing different patterns of cytokines and/or cytotoxic factors</td>
<td>Can be elicited by patch testing or intradermal test read after 48 h</td>
<td></td>
</tr>
<tr>
<td>Type 4a</td>
<td>Th1-Tc1 cells: IFN-γ, TNF-α</td>
<td>Contact dermatitis, tuberculin reaction</td>
<td></td>
</tr>
<tr>
<td>Type 4b</td>
<td>Th2 cells: IL-4/-13, IL-5, Eosinophils</td>
<td>Maculopapular rash, exanthema with eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Type 4c</td>
<td>Cytotoxic T-cells: Perforin, Granzyme-B, Granulysin</td>
<td>Contact dermatitis, maculopapular drug rash, Stevens-Johnson syndrome, Toxic epidermal necrosis</td>
<td></td>
</tr>
<tr>
<td>Type 4d</td>
<td>T-cells: CXCL-8, GM-CSF, neutrophils</td>
<td>Acute generalized exanthematous pustulosis</td>
<td></td>
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</table>

prior to the patch test; topical corticosteroids applied in large doses even away from the test site may have same effect as low doses of systemic corticosteroids.[8] Strong UV-exposure (e.g., exposure at seaside) prior to drug patch testing will diminish test reactivity.[6] However, anti-histamines do not interfere with test results and can be allowed during/prior to drug patch testing (cf skin prick test).

The results are then read at D2, at D3 and another reading is made at D7 if initial results are negative. Results are reported according to International Contact Dermatitis Research Group criteria[9] as: No reaction (0), Doubtful reaction; faint erythema (?), weak positive; palpable erythema, infiltration, papules (1 +), strong positive [Figure 1d]; erythema, infiltration, papules, vesicles (2 +), extreme positive reaction; intense erythema and infiltration and coalescing vesicles (3 +), irritant reaction (IR) of different types, and not tested (NT).

SPECIFIC ISSUES ABOUT DRUG PATCH TESTING

The selection of a patient for drug patch testing is important as the final results depend upon a number of factors (vide infra) which can influence interpretation and usefulness of this procedure.

Clinical types of cutaneous adverse reactions

As not all cutaneous adverse reactions will elicit positive results, drug patch testing is suitable for investigating only a select type of drug reactions [Table 2]. Figures 2-4 depict serious clinical forms of adverse cutaneous drug reactions and potential cases of drug patch testing. A review of published reports suggests that, drug patch testing is particularly useful in cases of acute generalized exanthematous pustulosis (AGEP, ≥50%), maculopapular drug rash (50-60%), anticonvulsant hypersensitivity

<table>
<thead>
<tr>
<th>Table 2: Drug patch test recommended as first line investigation</th>
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<tbody>
<tr>
<td>Valuable in</td>
</tr>
<tr>
<td>Reported positive results[2,5,10-15] %</td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis                      ≥50</td>
</tr>
<tr>
<td>Maculopapular (exanthematous) drug rash                          50-60</td>
</tr>
<tr>
<td>Anticonvulsant hypersensitivity syndrome                        70</td>
</tr>
<tr>
<td>Drug rash, eosinophilia, and systemic symptoms                  ≥72</td>
</tr>
<tr>
<td>SJS-TEN from anticonvulsants, sulfonamides, NSAIDs              100</td>
</tr>
<tr>
<td>Betalactam antibiotics (ampicillin, amoxycillin) sensitivity    39-54</td>
</tr>
<tr>
<td>NSAIDs induced fixed drug eruptions                             40-87</td>
</tr>
<tr>
<td>Contact and systemic contact dermatitis, and photocontact sensitivity ≥87</td>
</tr>
<tr>
<td>Less valuable in</td>
</tr>
<tr>
<td>Urticaria, pruritus, vasculitis, SJS-TEN due to allopurinol, acute phase of DRESS (due to unavailable clear skin for patch testing or iatrogenic immunosuppression)</td>
</tr>
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</table>

NSAIDs: Non-steroidal anti-inflammatory drugs, SJS-TEN: Stevens-Johnson syndrome-toxic epidermal necrolysis, DRESS: Drug rash, eosinophilia, and systemic symptoms

Figure 2: A patient of generalized exanthematous drug rash of anticonvulsant hypersensitivity syndrome (from carbamazapine) characterized by moderate fever, facial and peri-orbital edema, and prominently pruritic maculopapular rash that occurred during first 2 weeks of drug intake (may appear even 10-14 days after stopping it). She also eventuated to AGEP (note: Pustular lesions over face); it can also progress to DRESS if multi-organ involvement, lymphadenopathy and eosinophilia develop.
syndrome (70%), drug rash, eosinophilia, and systemic symptoms (DRESS, ≥72%), and SJS-TEN (up to 100%), betalactam antibiotics (ampicillin, amoxycillin) sensitivity (39-54%), non-steroidal anti-inflammatory drugs (NSAIDs) induced FDE (40-87%), contact and systemic contact dermatitis, and photocontact sensitivity (≥87%).\textsuperscript{2,5,10-15} On the other hand, it is less valuable in cases of immediate type of drug reactions, pruritus, vasculitis, some cases of SJS-TEN (e.g., due to allopurinol), and photodermatitis from systemic drugs.\textsuperscript{2,5,12,13,16} Patch testing is more reliable for eczematous type and (systemic) contact dermatitis or anti-convulsant hypersensitivity reactions, which in most instances is due to anti-convulsants, NSAIDs, sulfonamides or betalactam antibiotics.\textsuperscript{15}

**Putative drug(s)**

The most immunologic (Type B) drug reactions are due to anti-convulsants (carbamazapine, phenytoin, phenobarbitone, or lamotrigine), sulfones, sulfonamides, and co-trimaxozole, NSAIDs (paracetamol, diclofenac, piroxicam, metamizole), betalactum antibiotics (amoxicillin, ampicillin), and tetrazepam.\textsuperscript{3,5,10,13} The list of putative drugs is expanding by the day; allopurinol, minocycline, nevirapine, abacavir are few recent additions. Less common causes of drug reactions are due to acyclovir, valaciclovir, diazepam, clobazam, terbinafine, fluoroquinolones, paracetamol, glucocorticoids, pseudoephedrine, heparin, captopril, and radio contrast media.\textsuperscript{5,7,17} Although, allopurinol has emerged second most common (first being anti-convulsants) cause of SJS-TEN, patch test is usually negative.\textsuperscript{12,18} Table 3 lists some common drugs used for drug patch testing, however, there is no consensus protocol that includes all drugs for testing.

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**Table 3: Putative drugs for patch testing**

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Carbamazapine</th>
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<tbody>
<tr>
<td></td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td>Lamotrigine</td>
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<tr>
<td></td>
<td>Sodium valporate</td>
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<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Paracetamol</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
</tr>
<tr>
<td></td>
<td>Piroxicam (tenoxicam, meloxicam, lornoxicam)</td>
</tr>
<tr>
<td></td>
<td>Celecoxib, etoricoxib</td>
</tr>
<tr>
<td></td>
<td>Metamizole</td>
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<td>Non-Betalactam antimicrobials</td>
<td>Sulfonamides including co-trimoxazole</td>
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<td>Quinolones (ciprofloxacin, norfloxacin, moxifloxacin)</td>
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<td>Cephalosporins (cefadroxil, cephalexin)</td>
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<td>Miscellaneous</td>
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<td>Iodinated contrast media</td>
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**Test preparations, test vehicles, and controls**

Pure drug form should be used for patch testing whenever possible in concentrations of 1-10% in
petrolatum, water or alcohol. Drug patch test is low between 11% and 38% and the clinical usefulness varies across studies depending upon putative drug(s) and clinical features of the cutaneous adverse drug reaction. Although positive reactions have high predictive value, false-positive reactions are not uncommon. They may be due to IRs, which are frequent with drugs like sodium valproate even in 1% concentration or from cross reaction between drugs themselves, within their own metabolites, or the metabolite of one drug and that of another. Cross reactivity is frequent especially among aromatic anti-convulsants (carbamazepine, phenytoin, phenobarbitone), lamotrigine and valproic acid, among betalactum antibiotics, acyclovir, valaciclovir and famcyclovir, and oxicams. False-negative drug patch test reactions are not uncommon especially in patient having non-immune drug reactions, when patch test drug has poor percutaneous absorption, e.g. allopurinol, in the absence of concomitant factors like drug-virus (human herpes virus 6, HIV) interactions or the metabolite responsible for eliciting T-cell-dependent adverse reaction is not formed in the skin. Wrong selection of vehicle, inadequate drug concentration and exposure time, and inappropriate timing for drug patch test are some of other possible reasons for false-negative reactions.

While specificity and negative predictive value of drug patch test is not yet determined, false-positive results need to be considered for final interpretation of the results. Predictive value of negative reactions is low and will not automatically exclude the offending drug. Barbaud et al. observed 58% positive results on intradermal drug test among 60 patients with cutaneous adverse drug reactions having negative patch test with the suspected drug. It suggests that skin prick test and/or intradermal test will be useful when patch testing is negative. They also recommend immediate reading in urticaria-like drug reactions and delayed reading in other cutaneous drug reactions for accuracy.

Patch testing should preferably be performed on a previously involved skin or else a false-negative result is likely. Similarly, some locations may be inappropriate for patch testing and discretion must be
practiced. Drug patch tests can be particularly helpful in determining the culprit drug in eczematous drug reaction, systemic contact dermatitis, maculopapular drug rash, DRESS, FDE and sometimes in SJS-TEN. It is easy to perform and any commercial drug can be used for testing (cf intradermal/prick tests). Adverse reactions to drug patch test are rare and it has been used safely in children as well.[26] However, possible precipitation of acute drug reaction, sensitization for cross reacting drugs, and possibility of contact allergy are some of the issues of ethical importance. Sometimes, drug patch test reactions occur earlier than 2 days (e.g., after 24 h in abacavir), or as late as 6-7 days after testing as in case of glucocorticosteroids or betalactam antibiotics.[8] Additional readings of results are highly desirable in such cases. In cases of negative patch test results, oral provocation test is considered to be the only reliable method to identify the culprit drug as in fixed drug eruption. In such a situation, oral provocation is performed first with the least implicated drug followed by more likely causes. A refractory period is also known especially in cases of FDE and a delay before and between patch testing and oral provocation is recommended. Patch testing, alone or in combination with oral provocation test, have a legitimate place in identifying the drug responsible for adverse reaction, especially, when multiple drugs are used to check for cross-sensitivities to medications or to generate a list of safe drugs.

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Systemic skin whitening/lightening agents: What is the evidence?

Munisamy Malathi, Devinder M. Thappa

INTRODUCTION

The human skin color is one of the most perceptible phenotypic variations among humans and is determined primarily by the type and amount of melanin synthesized within melanosomes and the pattern of melanosome distribution within the melanocytes. Getting a lighter skin tone always draws a lot of interest, as for centuries, fair or light skin color has been a symbol of prominence, superiority and higher social ranking. In India, attitudes towards skin color have developed over more than 2000 years and reflect considerations of class and caste. Women especially Asian women are obsessed with fair skin and they would go to the ends of the earth to lighten their skin color as in most cases their marriage prospects or career opportunities are dominated by the hue of their skin. Hence, skin whitening products are a half a billion dollar industry today capitalizing on the insecurity of these individuals and currently, skin lightening is one of the most common forms of potentially harmful body modification practices in the world.

A host of skin lightening agents are available in dermatology and cosmetic market and newer agents are continuing to be introduced. A lot is known about topical skin whitening agents, but systemic skin whitening agents which are slowly gaining popularity do not have much evidence to their credit in the scientific literature. In this article, we have addressed the issues related to the use of these systemic skin whitening agents.

An overview of the pathway of melanin synthesis and the site of action of the most commonly used systemic skin whitening agent (glutathione [GSH]) is depicted in Figure 1. The mechanisms governing pheomelanin to eumelanin balance are dependent on L-cysteine, GSH and tyrosinase related protein expression. Thus, as observed in the figure, the switching from eumelanogenesis to pheomelanogenesis can be influenced by modifying the ratio between cysteine and GSH levels. Pheomelanogenesis preferentially proceeds under conditions of high cysteine concentrations and low tyrosinase activity.[1]

SYSTEMIC SKIN WHITENING AGENTS AVAILABLE IN THE MARKET

GSH

The most commonly used systemic skin whitening agent is GSH used alone or in various combinations, both as oral and intravenous formulations. GSH is an antioxidant synthesized in all mammalian cells from three amino acids-glutamate, cysteine, and glycine. It is also available naturally in watermelon, avocado, broccoli, spinach and tomatoes. GSH exists in cells mostly in the reduced form (GSH) which is constantly oxidized forming oxidized GSH and its supply is replenished by the action of GSH reductase. GSH is involved in various biochemical processes especially those involving scavenging of free radicals and detoxification of toxic compounds, it acts as coenzyme and helps in the transport of amino acids across the cell membranes.[1] Lower GSH levels are implicated in many diseases and GSH
has been tried in the management of Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, alcoholic hepatitis, atherosclerosis, acquired immunodeficiency syndrome, and chronic fatigue syndrome. It has been commonly used to combat the neuro- and nephrotoxicity associated with cisplatin chemotherapy and this is the only Food and Drug Administration (FDA) approved indication for the intravenous form of GSH. The role of GSH as a skin whitening agent was an accidental discovery when skin whitening was noticed as a side effect of large doses of GSH. This led to extensive studies establishing its role in melanogenesis and the recent use of GSH as systemic skin whitening agent.

GSH exerts its action as skin whitening agent at various levels of melanogenesis which include the following:[1,3]

- Interference with cellular transport of tyrosinase
- Direct inactivation of the enzyme tyrosinase by binding with the copper-containing active site of the enzyme
- Mediating the switch mechanism from eumelanin to phaeomelanin production as GSH is the major physiologic reservoir of cysteine and increase in cysteine levels results in switching of eumelanogenesis to phaeomelanogenesis [Figure 1]
- Quenching of free radicals and peroxides that contribute to tyrosinase activation and melanin formation
- Modulation of depigmenting abilities of melanocytotoxic agents.

GSH for skin whitening is available in both tablet and injectable form. When taken orally, GSH is hydrolyzed by intestinal and hepatic gamma-glutamyl transferase resulting in reduced bioavailability. Even when large oral doses were administered, it was found that most of the absorbed GSH remains within the gut luminal cells and only small and transient increases of GSH could be detected in the general circulation.[4] Thus, the effectiveness of exogenously administered GSH is hindered by its instability when crossing cell membranes and its rapid hydrolysis in the circulation by gamma-glutamyltranspeptidase found on the extracellular surfaces of cells.[5] On the contrary, intravenous GSH delivers very high doses directly into the systemic circulation, overloading the renal circulation.

Oral GSH is in the “generally regarded as safe” category of FDA and is usually marketed as a food or dietary supplement and hence it does not certainly need to be FDA or Bureau of Food and Drug (BFAD) approved. There are no provisions in the law for FDA to approve
dietary supplements for effectiveness before they reach the consumer. However, FDA has banned the use of intravenous form of GSH for skin whitening in view of commonly reported side effects like skin rashes, Stevens Johnson syndrome, toxic epidermal necrolysis, derangement in thyroid and renal function and severe abdominal pain.\(^6\)

Until date there is only one study published in English literature assessing the safety and efficacy of oral GSH as a skin whitening agent.\(^3\) It was a randomized, double-blind, two-arm, placebo-controlled study conducted on 60 medical students in Thailand. They found 500 mg/day orally administered GSH, for 4 weeks to cause significant skin whitening when compared to placebo and they observed no significant adverse events. However, there were many flaws in the study-plasma GSH levels were not measured (as bioavailability of oral GSH is low), limited study period of 4 weeks, no follow-up to determine when the skin melanin indices return to their baseline values, medical students were chosen (young, otherwise healthy population) and the study was conducted during their college time to ensure that sun exposures were minimal. Hence, the results may be applicable to only young, otherwise healthy Asian individuals.

The promoters of GSH promote it at a dose of 20 and 40 mg/kg/body weight/day which is divided into two doses with a maintenance dose of 500 mg/day.\(^7\) They claim that gradual systemic effect will be seen 1-3 months in medium brown skin, in 3-6 months in dark brown skin, in 6-12 months in very dark skin and in 2 years are more in black skin. Injectable GSH is given at a dose of 900 mg weekly by intravenous or intramuscular method and the sessions can be repeated 2-3 times a week. They claim skin whitening to occur as early as 2-3 weeks.\(^7\)

GSH is also combined with many other agents like vitamin C to increase its absorption, N-acetyl cysteine to boost its level, alpha lipoic acid and other antioxidants like vitamin E and grape seed extract. Some oral preparations have dangerous combinations like monobenzone which causes irreversible depigmentation and hydroquinone which is banned by FDA as a carcinogen.\(^8\)

**L-cysteine peptide**

Another agent promoted for skin whitening is L-cysteine peptide, which is claimed to be 3-5 times more potent than GSH and is BFAD approved.\(^9\) Natural sources of L-cysteine include poultry, yogurt, egg yolks, red peppers, garlic, onions, broccoli, Brussel sprouts, oats, and wheat germ. L-cysteine along with L-glutamic acid and glycine is the rate-limiting precursor in the synthesis of GSH peroxidase and has been found that high concentrations of L-cysteine reduced the tyrosinase activity and produced more pheomelanin by way of cysteinyl dihydroxyphenylalanine (DOPA), the building block of pheomelanin [Figure 1]. The cysteinyl DOPAs can be formed in two ways-directly by nucleophilic addition of cysteine to DOPA quinone or indirectly from GSH DOPA by action of gamma-glutamyl transferase and peptidase.\(^10-12\) Hence L-cysteine peptide is promoted as skin whitening agent but without much scientific evidence to support its use for this indication.

**Tranexamic acid**

Tranexamic acid (trans-4-aminomethyl cyclohexane carboxylic acid), a plasmin inhibitor, commonly used as a haemostatic agent owing to its antifibrolytic action is also promoted as a systemic skin whitening agent especially as oral or intradermal injections for melasma. The skin whitening effects of tranexamic acid was incidentally found when it was used in the treatment of aneurysmal subarachnoid hemorrhage. It is a synthetic derivative of lysine and its therapeutic role in melasma was first studied by Nijor as early as in 1979, but only limited data exist in the literature regarding its use in melasma. Plasmin, is a protease that enhances the intracellular release of arachidonic acid, a precursor of prostanoid, and also elevates alpha-melanocyte stimulating hormone (\(\alpha\)-MSH) processed from pro-opio-melanocortin. Both arachidonic acid and \(\alpha\)-MSH can activate melanin synthesis by melanocytes. Tranexamic acid by way of its antiplasmin activity depletes the keratinocyte pool of arachidonic acid involved in ultraviolet (UV) induced melanogenesis.\(^13-17\)

It has been used at a low dose of 250 mg twice a day for at least 3 months for the treatment of melasma and found to be effective.\(^15\) But, it is not safe to use it for a long duration in view of its anti-hemorrhagic property resulting in side effects like venous thromboembolism, myocardial infarction, cerebrovascular accidents and pulmonary embolism. It is contraindicated in patients with acquired defective color vision, an active intravascular clotting condition, and hypersensitivity to tranexamic acid.\(^15\) However, there is no scientific
data available demonstrating the role of tranexemic acid as an overall skin whitening/lightening agent. It is even being promoted as intravenous injection for skin whitening at a dose of 500 mg every week for 1 or 2 months and 500 mg every month for maintenance.[18] Tranexamic acid has been found to produce good synergistic effect when combined with ascorbic acid or its derivatives and L-cysteine.[17]

Miscellaneous agents
Apart from these, large doses of vitamin C, hyaluronic acid, epidermal growth factor and combinations of multiple natural extracts (natural collagen extracts, bearberry extract, Glycyrrhiza glabra extract, Lycopene, Kelp, olive leaf extract, hawthorn, jujube, sea buckthorn, starch, coix seed, pearl extracts, etc.,) are also promoted for skin whitening in the form of food or dietary supplements with no scientific evidence.

Nevertheless, there are few animal studies and in vitro studies demonstrating the role of natural extracts like irradiated green tea polyphenol,[19] proanthocyanidin-rich extract from grape seeds,[20] ellagic acid-rich pomegranate extract,[21] and coumarin extracts from the plant Angelica dahurica,[22] in inhibiting melanogenesis resulting in skin whitening thereby recommending these agents as oral preparations for skin whitening. Procyanidins (pycnogenol, grape seed extracts) and Polypodium leucotomos have been found to effective and safe in the treatment of melasma and to prevent UV A induced pigmentary changes respectively.[23] But there are no trials demonstrating their efficacy in the treatment of post inflammatory pigmentation or in improving the general skin color.

THE SCENARIO IN INDIA

In India, GSH is available as Dr. James GSH whitening pills[24] which contains 100% natural pure GSH with alpha T-acids costing 3500/- rupees for 60 capsules of 1000 mg, I-Fair tablets[25] which contains GSH in combination with vitamin C, vitamin E, grape seed extract, alpha lipoic acid, and glutanova 900 skin whitening injections[10] which contains GSH with vitamin C and collagen. These agents are being advertised in the internet and currently there are no market data available on the use of these agents by Indians. As mentioned in the introduction, most of Indian women’s marriage prospects are dominated by skin color paving way for irrational use of these agents by these women and may result in untoward effects. Hence, well conducted studies, establishing the role of these agents in skin whitening and documenting adverse events is the need of the hour.

PROBLEMS WITH SYSTEMIC SKIN WHITENING AGENTS
As already mentioned above, these agents are not FDA approved for skin whitening and no scientific evidence exists for their use. In addition, the injectable formulations are counterfeited and given by untrained people illegally and hence associated with the risk of sepsis, air embolism, transmission of human immunodeficiency virus, Hepatitis B, and use of non-sterile preparations that can lead to serious infections.

Another major question that remains unanswered as yet is that whether switching the normal machinery from eumelanin (which is protective against UV radiation) to pheomelanin (which photosensitizes UV-induced deoxyribonucleic acid damage as observed in cultured human melanocytes) by an external agent for long duration would result in an increased incidence of skin cancers.[26,27]

As a general rule, the promoters of the systemic skin whitening agents list lactation, heart disease and hypersensitivity as contraindications for all these agents. Since there are not much human or animal studies advocating the role of these agents in skin whitening, there is no data on the relative and absolute contraindications, the appropriate dosing schedule and the long term side effects.

ECONOMIC CONSIDERATIONS

In India, the dermatology market is worth 1642 crore rupees ($410 million) and fairness-directed skin lightening cosmetic market (which are considered as “fast moving consumer goods”) is 1000 crore ($250 million) resulting in a staggering 61% of the total dermatology market.[28] Companies manufacturing skin lightening products take advantage of the lax advertising laws and make unsubstantiated claims about their efficacy taking a horrendous toll on the consumers. The high-end skin whitening products are often labeled under the new quasi-pharmaceutical category called cosmeceuticals – a hybrid entity with pharmaceutical and cosmetic properties. This ambiguous labeling strategy allows promoters of high-end skin whitening and anti-aging products to make both pharmaceutical
and cosmetic claims. The marketing trends are designed in such a way so as to blur the lines between cosmetics and food categories and food and pharmaceutical categories, thereby helping in evading the regulatory constraints for these products, eventually enticing more consumers to consume these relatively expensive and poorly regulated products. Thus, their claims can neither be independently verified, nor can potential risks to consumers be assessed.[29]

**CONCLUSION**

The desire for white and fair skin is a global phenomenon and it is being highly capitalized by both the cosmetic and dermatologic industries. It is an essential role of the dermatologist to make the public aware that skin lightening agents may progressively revert back the facultative color to the constitutive level and normally this color change will not go beyond the constitutive level. If such a change is claimed, it should be considered to be dangerous as such alterations can become non-reversible resulting in vitiligo and may also predispose to other complications like skin cancer as the normal biochemical processes are altered. Till date, systemic skin whitening agents do not have much scientific evidence regarding their use and strict laws should be enforced to ban the use of these agents until well conducted randomized controlled trials are available ensuring the safety and efficacy of these agents.

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A 30-year-old woman presented with a 15-year history of two asymptomatic dells on her right cheek. There was no history of preceding acne or inflammatory skin disease.

Dermatologic examination revealed two 0.5 cm and 0.3 cm-sized, sharply-demarcated, skin-colored papules with cup-shaped central depressions, located on the zygomatic [Figure 1] and mandibular regions of the right cheek. On close inspection, follicular plugging was evident.

Histopathological examination displayed a partially well-circumscribed tumor in the dermis with an overlying sharp depression. The tumor was composed of small cords and islands of basaloid cells that showed connection to the follicular infundibulum. Tumor strands were surrounded by a desmoplastic fibrous stroma [Figures 2 and 3]. Several keratinous cysts and foci of dystrophic calcification were also noted. Immunohistochemically, the tumor cells stained positive with anti-pancytokeratin (CK), anti-CK15 and negative with anti-carcinoembryonic antigen (CEA), anti-CK7 and anti-epithelial membrane antigen antibodies. The tumor was focally immunopositive for CK20 antibody, indicating the presence of scattered Merkel cells.

**WHAT IS YOUR DIAGNOSIS?**

![Figure 1: A well-circumscribed umbilicated patch on the right zygomatic region](image1)

![Figure 2: Thin cords and islands of basaloid cells in a dense fibrous stroma (H and E, x100)](image2)

![Figure 3: Closer view of Figure 2 (H and E, x200)](image3)
Answer

Diagnosis: Desmoplastic trichoepithelioma

DISCUSSION

Desmoplastic trichoepithelioma (DTE) is a rarely encountered benign adnexal tumor with an estimated incidence of 2 in 10,000 skin biopsies.[1,2] The age range varies from 0 to 80. The lesion usually develops on the face of a young woman (71-85%).[2] The cheek is the most frequent site of affection (50%).[1-3] There is a propensity for DTE development on the right side of the face.[2] DTE presents as an asymptomatic, solitary, annular, firm, white to yellowish papule or as a sclerotic plaque smaller than 2 cm. The lesion has a thread-like raised and rolled border and a non-ulcerated central dell.[1,2] The clinical appearance may be reminiscent of basal cell carcinoma (BCC).

The histologic portrait in previous reports encompasses narrow strands of basaloid cells, keratinous cysts and desmoplastic stroma.[2] The well-demarcated solid tumor is situated symmetrically within the papillary and reticular dermis.[2-3] Small basaloid cells with prominent oval nuclei and scant cytoplasm are arranged in slender strands containing one to three rows of cells. There is often a focal connection to the overlying epidermis through the follicular infundibulum. The stroma surrounding the strands of basaloid cells consists of ample homogeneous eosinophilic collagen and multiple horn cysts. There is no cleft between the nests of tumor cells and sclerotic stroma. While palisading is lacking, epidermal hyperplasia may be noted.[2] Foreign body granulomas from broken cysts, areas of calcification or ossification might be observed.[2,4]

The list of differential diagnostic considerations embraces trichoadenoma, trichoepithelioma, syringoma, sebaceous hyperplasia, granuloma annulare, BCC, microcystic adnexal carcinoma and squamous cell carcinoma.[2] Differentiation from morphea-like BCC may be extremely difficult, especially when a lesion is sampled only in part. Immunohistochemical markers may help the pathologist to distinguish DTE and morphea-like BCC. In particular, identification of CK20-positive Merkel cells within the lesion, the presence of CK15 expression in tumoral cells and CD34 expression in peritumoral stroma, along with the absence of CEA androgen receptor and Periodic Acid-Schiff (PAS) expressions may support a diagnosis of DTE and vice versa.[2-4] So far, CK20 is the most reliable immunohistochemical marker in differentiating DTE from morphea-like BCC.[4] However, CK 20 expression in DTEs may be focal.[2-4]

Once the diagnosis is established, DTE may be clinically followed-up with an expectant policy.[1] Cryotherapy, dermabrasion or laser surgery may pose risks of recurrence and/or scar formation. Imiquimod has been used in two cases as an adjunctive therapeutic measure, but without apparent benefit.[5] In equivocal cases, the best treatment is complete surgical excision.[1] If there is a consideration of microcystic adnexal carcinoma or morphea-like BCC or if tissue preservation is crucial, Mohs micrographic surgery may be recommended.[1,2]

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Net Letter 1

Are dermatologists familiar with acronyms?

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Net Letter 2

Familial congenital generalized hypertrichosis

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Net Letter 3

Eosinophilic panniculitis after subcutaneous administration of sodium heparin

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Net Letter 4

De Sanctis-Cacchione syndrome

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Net Quiz

Erythematous indurated plaque lesions on the breast

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A 50-year-old female patient, who had retraction of the right nipple for 2 years and erythema in the same breast for 2 months, was referred to our clinic. Mammography and breast ultrasonography performed at the time of onset of nipple retraction were normal. Dermatological examination revealed three erythematous, mildly indurated plaque lesions on the right breast, one of which involved the areola [Figure 1]. The nipple was retracted. The patient had no subjective complaints. The right axillary examination detected several lymphadenopathies, as confirmed by ultrasonography. The histopathological examination of the skin biopsy revealed islands of tumor cells in the dermal lymphatics [Figure 2]. These infiltrations consisted of round-shaped atypical cells with vesiculated nuclei and marked nucleoli. In immunohistochemical studies, strong positive staining by low-molecular weight keratin (LMWCK) and epithelial membrane antigen (EMA) and non-specific staining by vimentin have been detected.

**WHAT IS YOUR DIAGNOSIS?**

![Figure 1: Three erythematous plaques on the right breast, one involving the areola](image1.png)

![Figure 2: Tumor islands consisted of atypical epithelium cells in the lymphatics (H and E, x200)](image2.png)
The book “Critical Care in Dermatology” by Inamadar and Palit is a valuable addition in critical care practice of Dermatology as an easy and handy document. It has a good description of common, uncommon, and rare dermatological emergencies which Dermatologists encounter in their clinical practice. There is a detailed description of each dermatological emergency: how to recognize it; how to assess the severity and details of management. It also gives a good overview of general measures in the management of these emergent situations, which are of critical importance. There is a full chapter dedicated to Fluid, Electrolyte and Nutrition Therapy which is often a challenge for Dermatologists, since many are not familiar with the finer details of these therapies and the detail of the monitoring techniques and procedures during the management of these emergencies. The book also describes sample collection methods from different sites in critically ill patients for appropriate diagnosis and management. The issue of nursing care in Dermatological emergencies, which is an over-sighted aspect in the management of such emergent situations, has been well emphasized and appropriately detailed. The concept of Dermatological Intensive Care Unit is well highlighted in the book with details of necessary equipments needed for such set-up. A dedicated chapter on the Drugs used in Dermatological Emergencies would also be handy for treating physicians, to critically review the different aspects of the drugs including doses, adverse effects, drug interactions etc., Authors have also included a chapter on Drug Therapy in patients with renal and hepatic impairment which may at times be the situations in these patients. A chapter on Drugs in Pregnancy and Lactation appears to be an unnecessary avoidable intrusion in the book. More appropriate would have been the inclusion of management of Dermatological Emergencies in Pregnant and Lactating women which may at times be complex and challenging. At places in the texts, the sentences are incomplete, lack systematic presentation, and flow. The text matter at places is disjointed. Also there is repetition of texts at different places which could have been avoided. The skin biopsy has often been mentioned as a rapid diagnostic technique which at many centers is often not available for such purpose and there are no histopathological details of the various conditions where biopsy has been recommended or mentioned, to be of help to diagnosis the condition. At places, the tables are appearing before the text which makes reading of the book uneasy. Sometimes, tables appear at different places then the texts, leaving the readers wonders as to why these could not have been placed close to the text. “Why a particular condition is an emergency” good for the beginners to recognize condition as an emergency and manage it appropriately.

Overall, the book may be of value to Dermatologists working in a hospital setting and for trainees. Reducing the number of tiny illustrations on the front page, avoiding shades of color on the top of each page and slightly larger font-size of the text could have made the book more reader friendly.

High-dose intravenous immunoglobulin (IVIG) have been shown to be effective in treating severe autoimmune diseases that are refractory to standard immunosuppressive therapy. Although considered effective and safe in treating autoimmune blistering diseases, a clear evidence for its therapeutic effect besides case reports and case series is missing.

A retrospective analysis of 16 patients (10 patients with pemphigus vulgaris, 3 with pemphigus foliaceus, and one patient each with paraneoplastic pemphigus, bullous pemphigoid, and paraneoplastic bullous pemphigoid), refractory or relapsing disease under immunosuppressive combination therapy with at least two immunosuppressive drugs and who had received IVIG therapy for at least six full cycles, between January 2004 and July 2011 was done. The mean age and the mean duration from diagnosis to initiation of IVIG therapy was 50.4 years and 40.8 months, respectively. Patients had a mean of 2.9 immunosuppressive drugs prior to initiation of IVIG therapy. High-dose IVIG was administered at a total dose of 2 g/kg body weight intravenously per cycle over 2 days after ruling out the contraindications. Patients received IVIG every 4 weeks, and prior to discontinuation of IVIG the time between the cycles was extended to 5 or 6 weeks.

Efficacy of IVIG therapy was assessed with changes in skin symptoms, changes in autoantibody titers, and tapering of steroid dose. Laboratory blood tests including antibasement membrane antibodies and anti-intercellular epidermal antibodies were routinely performed. To measure efficacy of IVIG therapy, a score for each 6 months during the total period of 24 months was used:

- (Very good) – no skin symptoms; autoantibody titer: No change or lower titer,
- (Good) – skin symptoms ameliorated; autoantibody titer: No change or lower titer,
- (Satisfactory) – skin symptoms unchanged; autoantibody titer: No change or higher titer,
- (Unsatisfactory) – skin symptoms deteriorated; autoantibody titer: No change or higher titer.

By the end of the 24-month observational period, most of the patients were still receiving IVIG. The mean total number of cycles per patient was 38.6. Adverse events were recorded in 87.5% of patients and in 56.3% of total infusion cycles. Headache (43.8%) and fatigue (43.8%) were the commonest side effects recorded. Only one patient reported petechiae after a single infusion cycle. Majority of patients had a very good score (43.8%, 75%, 61.5%, and 58.3%, respectively) in all of the four half-year periods. Also tapering of steroids up to a mean reduction of 75.8% in starting dose was possible without relapse in most patients.

Comment: IVIG is prepared from the pooled plasma of donors. Although initially used in the treatment of primary immunodeficiency syndromes, recently its use has been widely explored as an off-label indication in a variety of autoimmune and inflammatory conditions across multiple specialties.

Treatment of autoimmune bullous skin diseases can often be challenging. The treatment options primarily comprise systemic corticosteroids and a variety of immunosuppressants. Current treatment strategies are effective in most cases, but side effects of long-term immunosuppressive treatment are a limiting factor in some cases.

In addition, few patients fail to respond or experience frequent relapses. Some of the immunosuppressives have a long latency before benefit begins. The situation becomes all the more problematic in children for the fear of growth retardation. Secondary infection, which may be either systemic or localized to the skin, may
occur because of the use of immunosuppressants and the presence of multiple erosions. Unlike most therapies for blistering disorders, IVIG is not immunosuppressive and has a favorable side effect profile.

This has allowed its use to expand dramatically over the past decade. It is generally accepted that the use of IVIG should be limited to patients who (1) fail conventional therapy; (2) have side effects or contraindications to conventional therapy that limits its use; and/or (3) have rapidly progressive disease or progressive disease despite conventional therapy.

This study demonstrates tapering of steroids up to a mean reduction of 75.8% from starting dose without relapse in most patients. Most of the reports utilizing IVIG at a dose of 2 gm/kg/cycle have shown a positive clinical outcome, decrease in pathogenic autoantibodies, and a steroid-sparing effect.

It has been well documented that IVIG causes a rapid decline in pathogenic autoantibody levels following which there is often a rebound increase, as in plasmapheresis. It has been hypothesized that use of IVIG along with rituximab or cyclophosphamide would be more beneficial in causing decline in pathogenic antibodies, suppressing the rebound increase and providing a sustained long-term remission with relatively low infectious complication rates.

In general, most published reports on IVIG have been retrospective analysis. There is a paucity of well-designed prospective trials. There is a need for randomized controlled trials for determining the efficacy and adverse effects of IVIG in the treatment of autoimmune bullous skin diseases.


Axillary hyperpigmentation is a frequent cause of cosmetic consultation among dark-skinned women from tropical areas, including Latin America. Currently, there is no widely accepted treatment for the disorder. It is usually treated with bleaching agents because it is considered a variant of inflammatory hyperpigmentation. This was a 9-week, randomized, double-blind, left–right axilla, placebo-controlled trial study conducted to assess the efficacy of niacinamide 4% and desonide 0.05% emulsions in the treatment of axillary hyperpigmentation.

Twenty-four women aged 19-27 years with hyperpigmented axillae (phototypes III-V) were randomly assigned to receive the study treatments in the axillary region. Improvement was assessed at baseline, then clinically and by colorimetry 9 weeks later. Quantitative evaluation including melanin, inflammatory infiltrates, NKI/BETEB, CD1a, CD68, and collagen type IV content was performed by histochemistry and immunohistochemistry, assisted by computerized morphometric analysis.

Both niacinamide and desonide induced significant colorimetric improvement compared with placebo; however, desonide showed a better depigmenting effect than niacinamide. A good to excellent response was achieved in 24% of cases for niacinamide, 30% for desonide, and 6% for placebo. Side effects, including local erythema, burning, pruritus, infection, and skin atrophy, were absent during the trial. In addition to the associated inflammatory cell infiltrates, a physical discontinuity of the epidermal basal membrane was found which improved after exposure to both drugs and was more evident in the desonide group.

Comment: Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury. It can arise in all skin types, but is more frequent in individuals with darker skin (Fitzpatrick skin types IV to VI) as the melanocytes of darker-skinned individuals show an exaggerated response to cutaneous injury. PIH can have a significant psychosocial impact, which is well supported by various epidemiological studies that depict dyschromias. Axillary hyperpigmentation has not been extensively studied due to its primarily cosmetic nature and lack of any major and significant health implications. It has been proposed that axillary skin darkening is best defined as mild PIH, characterized by increased epidermal melanin production, following mild irritation or stimulation of the skin. The treatment of hyperpigmentation in these patients has remained challenging for dermatologists.

Axillary skin is distinctly different from those of other body sites, as it has reduced barrier integrity. Studies have shown cholesterol, ceramide 3, and lactic acid levels to be increased, and natural moisturizing factor amounts to be lower, cornified envelopes to be smaller.
indicative of a shorter stratum corneum turnover, compared with the volar forearm.

Although the precise pathogenesis is unknown, it is thought to result from cytokines, inflammatory mediators, and reactive oxygen species. In some individuals, the axillary skin may face additional challenges including leaching of lipids and proteins from the stratum corneum by cleansing surfactants, or additional irritation induced by shaving and plucking which further impairs the natural barrier to exogenous irritants. Histological evaluation of female Filipino axillary skin has revealed that the trauma of underarm hair plucking is associated with melanosome leakage into the dermis and hence increased pigmentation, as well as mononuclear cell and macrophage infiltration.

This study reveals that niacinamide and desonide have depigmenting properties in women with axillary hyperpigmentation along with the added advantage of improvement in the physical discontinuity of the epidermal basal membrane. However, multicentered trials including a large number of patients would be helpful in providing a better interpretation.


Photoepilation with lasers or intense pulsed light (IPL, 590-1200 nm) sources is a widely used efficient and safe treatment modality for the removal of unwanted hair. Devices currently in use work on the basis of the selective photothermal destruction of hair follicles, which is based on the principle of selective photothermolysis. This randomized controlled trial (RCT) was undertaken to compare the efficacy, side effects, and patient-rated efficacy of two popular light devices for hair removal, a diode laser (DL) and an IPL source.

IPL and DL treatments were evaluated in 30 participants with a mean age of 33.7 years (skin types II–III) with unwanted axillary hair. Six treatments with each device were carried out at 4-week intervals. The two axillary regions of each patient were randomized to the two competing procedures. After each laser treatment, study subjects were evaluated for immediate side effects, such as burning, edema, and blistering. A visual analog scale (VAS) ranging from 0 to 10 was used for the self-assessment of pain (0 = no pain, 10 = maximum pain) at every treatment visit. The mean score for all six visits was obtained. For the quantitative evaluation of hair growth, the three regions of interest of each axillary region were photodocumented at each visit with a handheld dermatoscope. Final assessment was conducted 12 months after the last treatment by means of hair counts using close-up photographs. The primary endpoint was reduction in hair growth, analysed on an intention-to-treat and last-observation-carried-forward basis (n = 30), and secondary endpoints were patient-rated efficacy, treatment-related pain, adverse effects, and treatment duration.

All participants completed the 3- and 6-month follow-up evaluations (visits 7 and 8), but only 25 volunteers were available for the 12-month follow-up (visit 9). Both devices significantly reduced hair counts. Mean reductions from baseline (3 and 12 months after the last treatment) were 59.7% and 69.2% for DL and 42.4% and 52.7% for IPL treatment (P < 0.01), respectively. DL treatment induced significantly more pain [3.7 ± 2.1 (DL) vs 1.6 ± 1.4 (IPL); P < 0.01; VAS] but could be conducted faster [33.1 ± 3.8 s (DL) vs 40.1 ± 5.0 s (IPL); P < 0.01]. No severe side effects were observed for either therapy.

Comment: Advances in laser technology have led to the establishment of laser hair reduction as a safe modality for the treatment of unwanted hair on any body part. An ideal patient has thick dark terminal hair, white skin, and a normal hormonal status. There is a paucity of data regarding the safety and efficacy of lasers in dark-skinned individuals.

Studies in the past have compared diode and ND: YAG laser in terms of efficacy for hair reduction with most of them showing DL to be more comfortable and efficacious. However, without the use of topical anesthetics, patient preference might be based on pain level during the treatment session.

Few studies done in the past have directly compared long-term outcomes of lasers with IPL with both the lasers and light devices showing similar long-term efficacy contradicting the results of this study. Current long-term evidence on efficacy of IPL is sparse. Few trials comparing diode with IPL have shown similar efficacy at 6 months after treatment contrary to the results in this study.

In this study, all sessions were repeated at 4-week intervals. The resting phase for axillary hair tends to be longer when compared with the scalp and beard.
hair. Doing the sessions too frequently might lead to a temporary suppression rather than destruction of hair follicle. Controlled trials would be required to differentiate the hair reduction in the long term achieved when sessions are done at 4 weekly intervals versus increasing the gaps after second session.


Earlobe keloids are benign, fibrous proliferations occurring in predisposed persons at sites of cutaneous injury (ear piercing, burns, or surgical procedures). Twelve consecutive patients with earlobe keloids were treated with a combination of surgery and cryosurgery. The surgical procedure consisted of shaving after local anesthesia leaving 1-2 mm of the remaining lesion at the borders. Cryosurgery (liquid nitrogen spray) of the underlying tissue followed it. One cycle of freezing was performed (freezing time 60 s). Patients were evaluated 7 and 30 days after the surgical procedure. At day 30, cases with persistent keloid lesion received adjuvant therapy with intralesional injection of triamcinolone acetonide (10-20 mg/mL). Monthly evaluation was done. The mean posttreatment follow-up was 12 months. Major response, moderate response, and failure was defined as 80%-100% reduction in keloid thickness, 50%-80% reduction in keloid thickness, and improvement of less than 50% or complete relapse after treatment, respectively.

After 1 year, major and moderate response were observed in 9 cases (75%) and 2 cases (16%), respectively; 1 case had relapse 5 months after surgery. The number of intralesional triamcinolone injections varied from none to 4.

Comments: Earlobe keloids are benign fibrous proliferations characterized by an excess of collagen deposition. They occur in predisposed individuals at sites of trauma, ear piercing, burns, or surgical procedures. The incidence is higher in blacks and Asians when compared with Caucasians.

They are commonly encountered in day-to-day clinical practice and pose a challenging management problem and distinctive cosmetic implications. Clinically, they appear as shiny, smooth, globular growths on one or both sides of the earlobe. Pruritus, pain, and paresthesias can be another source of distress for some of these patients.

Various therapeutic modalities are available for treatment of keloids. There is no consensus regarding the optimal or best management of keloids. Surgical excision alone has been found to have a low success rate with a high incidence of recurrence in previous studies. Intralesional injection of corticosteroids is one of the mainstays in the management of earlobe keloids. Monotherapy with intralesional injection of steroids has been found to alleviate the subjective symptoms in most of the studies with variable success in improving the objective symptoms.

In the recent literature, surgical excision along with adjuvant therapy is recommended. There is no standardized protocol regarding the administration of intralesional corticosteroids. Some have advocated the instillation of steroids after removal of the sutures followed by weekly or fortnightly injections. Few have also advocated the use of intralesional steroids prior to surgical excision.

Cryosurgery as monotherapy for the treatment of earlobe keloids has shown diverse results. The recently introduced intralesional cryoneedle method has been found to be simpler and safer to use, requiring less postoperative care.

In this study, major response was observed in majority of the cases at 1 year of follow-up with shaving, cryotherapy, and intralesional steroids. The success rate of combination of surgery and triamcinolone acetonide injection has shown great variation across different studies with some exhibiting unsatisfactory response. Here the treatment modality consists of three different treatment techniques. The favorable response illustrated probably reflects the synergism of the combinations. However, in a given patient, the location, size, depth, and duration of earlobe keloids are critical factors in deciding the individualized modality of treatment.

Although this study reveals good comprehensive results, studies dealing with duration of keloids comparing with various treatment responses need to be carried out.


Paraneoplastic pemphigus (PNP) is a multiorgan disease characterized by antibodies against plakins, desmogleins,
and the alpha-2-macroglobulin-like-1 (A2ML1) protein, in association with an underlying neoplasm. This study was undertaken to compare the diagnostic value of different laboratory techniques in the serological diagnosis of PNP by performing immunoblotting, ELISA for envoplakin (EP ELISA), anti-Dsg1, anti-Dsg3, BP180, BP230, indirect immunofluorescence (IIF) on rat bladder, radioactive immunoprecipitation (IP), and a nonradioactive combined IP-immunoblot assay on the sera of 19 PNP (median age of 56.6 years) and 40 control patients. The diagnosis of PNP was made if patients fulfilled the revised criteria proposed by Anhalt in 2004 and Zimmerman in 2010.

Sensitivities for anti-EP ELISA, rat bladder IIF, immunoblotting (IB), radioactive IP and nonradioactive IP were 63%, 74%, 89%, 95%, and 100%, respectively, with specificities ranging from 86% to 100%. Low sensitivity and specificity were observed with BP180- and BP230-ELISAs.

**Comment:** PNP is a distinct autoimmune blistering dermatosis occurring in association with various neoplasms. The clinical features consist of recalcitrant, painful oral erosions that may be accompanied by polymorphic cutaneous eruptions and systemic involvement. It is characterized by the presence of autoantibodies against desmoglein 3 (Dsg3) (130 kd), desmoglein 1 (Dsg1) (160 kd), envoplakin (210 kd), periplakin (190 kd), desmoplakin I (250 kd), desmoplakin II (210 kd), bullous pemphigoid antigen 1 (BPAG1) (230 kd), plectin (>400 kd), and a previously unidentified 170-kd protein which has recently been identified as A2ML1, a broad-range protease inhibitor expressed in stratified epithelia.

Histological findings vary considerably according to the clinical presentation and age of the lesions with predominant suprabasal acantholysis in noninflammatory blisters, whereas interface and lichenoid dermatitis in erythematous inflammatory maculopapular lesions. DIF is negative in half of PNP patients and false negatives are also common, attributable to lichenoid lesions and necrotic tissue in the mucosal biopsies. The presence of autoantibodies to plakins is a characteristic feature with highest specificity for envoplakin and periplakin followed by desmoplakins. Plakin autoantibodies, however, have been found in other conditions such as pemphigus vulgaris, pemphigus foliaceous, erythema multiforme, and toxic epidermal necrolysis, hence demonstration of antiplakin antibodies alone is not sufficient to point toward the diagnosis of PNP.

IP has been found to be the most sensitive and specific test for demonstrating antiplakin antibodies in most of the studies, qualifying as a major diagnostic criteria for PNP. However, tedious nature, cost, and lack of easy availability are the limiting factors. This study shows sensitivity of radioactive IP assay to be superior to IB, IIF on rat bladder, and EP-ELISA. Also, the nonradioactive IP showed marginally higher sensitivity than the radioactive IP. In the absence of IP, combination of IB and rat bladder-IIF may be used as the first serological test for confirming the diagnosis of PNP.

However, more studies with larger number of patients are required to support the findings, which would be of a substantial help in accurately diagnosing this often-fatal disease with a myriad of variable cutaneous morphologies and the morbidity of recalcitrant mucosal lesions.


Female pattern hair loss (FPHL) is one of the most common causes of hair loss, affecting 50% of women in the age of 50 years. Treatment of FPHL is frustrating for both patients and doctors. This study including 126 female patients with FPHL was carried out to evaluate the efficacy and safety of mesotherapy using dutasteride-containing preparation. The patients were classified into two groups: Group I (86 patients) (mean age 34.1 ± 6.6 years) and group II (40 control patients) (mean age 34.8 ± 7.2 years) injected with dutasteride-containing preparation and saline, respectively. Patients received 12 sessions over a period of 16 weeks and were evaluated at the 18th week by photographic assessment, hair pull test, hair diameter, and patient self-assessment. Ultra structural evaluation was done for three patients using five of the randomly epilated hairs from the vertex as described by Wyatt and Riggott, before and at the 18th week using scanning electron microscope. Photographic improvement was seen in 62.8% of patients compared with 17.5% in control group. Significant improvement in mean hair diameter and
decline in mean number of epilated hairs were seen in group I. Side effects were minimal with no statistically significant difference between the two groups. Ultra structural examination of pretreated hairs revealed absent cuticle in one patient and focal destruction of the cuticle in the second patient, which reappeared in both after therapy. There was a negative correlation between degree of improvement and duration of FPHL ($P < 0.05$).

**Comment:** FPHL is the most common cause of alopecia in women characterized histologically by increased numbers of miniaturized hair follicles. Although medically benign, the impact is predominantly psychological leading to distress, low self-esteem, depression, and impaired quality of life in a significant number of affected females.

The goal of treatment is to arrest the progression of alopecia and stimulate new hair growth. Two main pharmacological options currently widely used are antiandrogens and minoxidil, which need to be continued indefinitely to attain and maintain response.

Mesotherapy has gained a lot of attention in recent past; however, the scientific basis is not established. The US FDA in view of lack of documented evidence has not yet approved it. On theoretical grounds, it can be hypothesized that dutasteride might be more efficacious than finasteride as the latter being a selective inhibitor of type 2 isoenzyme of 5-alpha reductase has the capability to reduce serum dihydrotestosterone levels by about 70%, whereas dutasteride inhibits both isoenzymes inducing more than 90% reduction in the dihydrotestosterone levels. Longer half-life of dutasteride when compared with finasteride has been a limiting factor for the former’s use.

In this study, dutasteride administered by meso therapy demonstrated significant increases in target area hair count in comparison to placebo, as early as 12 and 24 weeks. In few studies assessing the efficacy and safety of five alpha inhibitors in androgenetic alopecia, dutasteride was found to be superior to finasteride at 12 and 24 weeks in male pattern hair loss. Also, few reports showed noteworthy response with dutasteride in patients with limited improvement after 6 months of finasteride. This study results reiterate the above findings.

Current treatment options are limited, and even in positive responders a considerable time delay occurs before improvement is apparent. In cases of advanced alopecia (Ludwig grade III) and failure with aforementioned medical therapies, surgical management remains an important option. Dutasteride may be considered as an additional treatment option, following further studies in cases of grade I and II FPHL.

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There has been an ever-increasing demand for aesthetic procedures to reverse the effects of aging, particularly in the facial area. Recently, topical nifedipine has been found to have anti-wrinkle effects. The aim of this study was to confirm the anti-wrinkle efficacy and tolerability of a 0.5% nifedipine-based topical formulation.

A randomized study was conducted in 20 healthy female volunteers aged between 45-60 years with moderate to moderately severe facial wrinkles and Fitzpatricks skin phototypes II-IV. Ten volunteers (group A) applied a cream containing nifedipine at a concentration of 0.5%, hyaluronic acid, collagen, and vitamin A and E, and the other 10 (group B) applied a good moisturizer, containing hyaluronic acid, collagen, and vitamin A and E. Patients in both groups were instructed to apply measured amounts (0.1 g) of topical formulations on forehead, nose-geniene, periocular and perilabial wrinkles, twice daily for 3 months after washing the face with the same mild facial cleanser. All parameters were evaluated at baseline (T0), and then 30 (T1), 60 (T2), and 90 (T3) days later. The aesthetic improvement was evaluated by a blinded investigator using the Wrinkle Severity Rating Scale (WSRS) with grade 1 indicating minimum severity and grade 5 indicating maximum severity. In group A, mean WSRS scores at T1 (2.79), T2 (1.99), T3 (1.84) were approximately 1.38, 1.93, and 2.09 times lower than mean WSRS score at T0 (3.85), respectively. In group B, the mean WSRS score at T0 was 3.78, at T1 3.41, at T2 3.42, and at T3 3.36. Post-treatment WSRS score was significantly lower than the baseline WSRS score only in the nifedipine group.

Improvement in skin hydration was found to be more in group A than in group B at the end of the study period of 90 days. Also, the use of nifedipine cream in group A resulted in significant overall lightening of the skin compared with baseline and the control group. The absence of de-pigmenting agents in the tested product suggests a possible role of nifedipine in skin lightening. No significant change in blood pressure and heart rate were recorded during this study.

Comment: Both intrinsic and extrinsic factors influence the aging process. Extrinsic factors include sun exposure, repetitive or exaggerated mimic expressions, gravity, and smoking. Reactive oxygen species (ROS), a byproduct of both environmentally induced and intrinsic aging, lead to a cascade of biochemical reactions within the skin, resulting in the production of matrix metalloproteinases (MMPs) and proinflammatory cytokines. Reduction in collagen and elastin and a loss in hydration are the main structural changes in skin resulting from aging leading to wrinkling. Wrinkles can be divided into four main types: Atrophic crinkling rhytids, permanent elastotic creases, dynamic expression lines, and gravitational folds. Each type usually develops on specific skin regions exhibiting distinct micro-anatomical characteristics. However, the most important pathogenic mechanism is the chronic contraction of mimic muscles.

Nifedipine is a dihydropyridine-type calcium channel blocker that blocks the transmembrane influx of calcium ions into muscle cells inhibiting their contraction, thus accounting for its efficacy in the treatment of facial wrinkles. In nifedipine group, there was a greater improvement in viscoelastic properties of skin, and another significant effect observed was skin lightening. Authors have not provided explanation for the observed skin lightening effect. Its poor percutaneous penetration combined with its rapid metabolism in the skin limits its systemic absorption and side-effects. So, topical nifedipine preparations can prove to be an economical, effective, and convenient means of anti-wrinkle treatment.

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Further in-depth studies are needed to evaluate the anti-aging effects of topical nifedipine over longer treatment period and its possible role not only in skin rejuvenation, but also in the prevention of cutaneous aging by increasing skin hydration and elasticity.


The biologic agents are highly efficacious in the treatment of psoriasis and psoriatic arthritis. However, their use is associated with an increased risk of developing active tuberculosis (TB). All patients should be screened for latent tuberculosis infection (LTBI) prior to initiating therapy. This article reviews the current recommendations for screening and chemoprophylaxis of LTBI in Italian psoriasis patients treated with biologics.

LTBI is defined by the presence of *Mycobacterium tuberculosis* without clinical symptoms, and bacteriological and radiographic signs of disease. Only about 10% of these patients develop active TB, immunosuppression being a major risk factor for activation. Among the anti-TNF-α agents, the risk of LTBI activation is three to four times higher with the monoclonal antibodies (adalimumab, infliximab, and certolizumab) as compared to etanercept. There are no reports of LTBI reactivation with alefacept. The risk of LTBI with ustekinumab is lower than that observed with anti-TNF-α therapy. However, screening for LTBI is recommended before starting any biologic therapy for psoriasis.

According to the recommendations of an expert working group of Italian dermatologists, screening process for LTBI includes taking complete medical history, chest X-ray (CXR), purified protein derivative skin test (PPD), and interferon γ release assays (IGRAs). History pertaining to age, TB vaccination, previous TB infections, family history of TB, exposure to possible sources of infection, and any recent immunosuppressive or long-term antibiotic therapy should be taken. CXR should be performed in two projections and interpreted by a radiologist (although US National Psoriasis Foundation consensus statement recommends an X-ray only if immunologic tests are positive). Indurations larger than 5 mm are considered positive in the PPD test. Although having good sensitivity, false negatives can result from immunosuppression as a consequence of an autoimmune disease, medication, and age. False positives test can result from vaccination with bacillus-calmette-guérin (BCG) and exposure to non-tuberculous mycobacteria. A two-step test, also known as a booster PPD, has been suggested, in which a second PPD is administered 1-3 weeks after the first to provoke an anamnestic response to reinforce weakened immune memory. This is useful in older patients or in patients who are at high risk of infection but show a negative result on the first PPD test. *In vitro* immunological tests for LTBI include Quantiferon and T-SPOT.TB, collectively referred to as IGRAs. These assays correlate better with TB exposure, and they are not influenced by vaccination with BCG or previous exposure to non-tuberculous mycobacteria. They also have a higher specificity. IGRAs employing a cocktail of antigens may be more sensitive than PPD in immunosuppressed patients.

A positive IGRA test is an indication for prophylactic treatment, independent from the results of other tests. The situation is less clear when the IGRA and radiology results are negative, but the PPD is positive. In this case, it is necessary to carefully evaluate the individual situation. If the medical history does not suggest a risk, the PPD result is generally considered a probable false-positive, especially if there is a history of BCG vaccination. However, chemoprophylaxis may still be initiated if a false-negative IGRA result is suspected. If the X-ray results are positive while the other tests are negative, the patient should be referred to a pulmonologist for further evaluation.

For prophylactic treatment, in most cases, isoniazid at a dose of 300 mg/day for 9 months is recommended. The combination of rifampicin/pyrazinamide is not recommended due to the risk of hepatotoxicity. Anti-TNF-α therapy can be started at least 1 month after initiating prophylactic therapy.

**Comment:** The advent of TNF-α inhibitors as a treatment modality in psoriasis is a significant step forward in its management. However, a significant roadblock still remains due to the risk of developing TB in patients with LTBI preventing the optimal utilization of this modality. Animal studies have shown that TNF-α inhibition impairs inflammatory cell trafficking and granuloma formation. Currently recommended screening for LTBI, typically, risk assessment, tuberculin skin testing (TST), and CXR used prior to anti-TNF-α treatment can significantly reduce TB activation rates, but newer screening tests like IGRAs may enhance screening efficacy further.
Patients positive on screening who are treated with isoniazid and subsequently receive anti-TNF-α treatment still have approximately 19% risk for TB.

IGRA test has a better sensitivity and specificity than TST in detection of LTBI and is superior for predicting TB infection, especially in immunosuppressed patients. In a country like India where BCG vaccination is routinely administered to all in infancy, IGRA test has still higher utility, and the requirement for TB chemoprophylaxis can be significantly reduced. A strategy of simultaneous testing to optimize diagnostic sensitivity is suggested in the clinical use of biological drugs. IGRA’s performed post-TST was elevated since day 3. So, it is advisable that when using a two-step screening strategy, it is better to perform an IGRA within 3 days after performing the TST.

A higher rate of TST positivity is found in patients of psoriasis being screened for LTBI than the corresponding inflammatory bowel disease (IBD) patients, which may be due to the priming of their clinically healthy skin to overreact to a broad-spectrum of antigenic triggers, including M. tuberculosis derived antigens and also there is a higher degree of drug-induced immunosuppression in patients of IBD. It seems reasonable to propose that injection of tuberculin antigens into the unaffected skin of patients with overt plaque psoriasis triggers augmented inflammatory reactions resulting in stronger TST, and adherence to the widely accepted TST-based recommendations for the diagnosis of TB leads to overdiagnosis of LTBI in patients with plaque psoriasis.

In countries, where TB prevalence is very high, the criterion of LTBI diagnosis may be less valuable and the guiding principle for LTBI treatment may not be as strict as in the western countries. Unlike active disease, monotherapy is often used in treating LTBI. The lower bacillary load in LTBI reduces the chances of developing resistant mutants, although this possibility cannot be fully excluded. Isoniazid at a dose of 5 mg/kg (upto 300 mg/day) is used for chemoprophylaxis for a period of 9 months, and the anti-TNFα therapy can be given at least 1 month after initiating prophylactic therapy.

The screening protocols for LTBI need to be applied in a way that there are less false positives so as to avoid denial of treatment to candidates who are eligible for anti-TNF-α therapy. It should also be sensitive enough to identify patients at risk of LTBI activation. The tendency of patients with psoriasis to have higher number of false-positive TST results and the reduced diagnostic specificity of the TST in BCG-vaccinated populations may greatly diminish the value of traditional screening method of TST in psoriatic patients in India. TST needs to be combined with clinical history and supportive evidence from CXR and IGRA’s to help decision-making while screening for LTBI in psoriasis patients being considered for anti-TNF α therapy.


Plantar hyperhidrosis (PLH) is an emotionally distressing condition. Several anti-cholinergic drugs have been tried for its treatment in past, but their use is limited by their adverse effects. Oxybutynin is an anti-cholinergic drug, which is primarily used for treating urinary disorders and diminished sudorenesis is one of its side-effects. The aim of this study was to evaluate the effectiveness and patient satisfaction with the use of oxybutynin when given at low doses for treating PLH. Thirty-five patients (aged between 18-71 years) with PLH were treated with oxybutynin, of these 30 (female-26, male-4) completed the study. They also had hyperhidrosis at other sites on the body, palmar in 25 (83.3%), axillary in 13 (43.3%), craniofacial in 5 (16.6%), and thoracic and abdominal in 5 (16.6%). During the first week, patients received 2.5 mg of oxybutynin once a day, 2.5 mg twice a day from the eighth to the 42nd day, and from the 43rd day till the end of 12 weeks, 5 mg twice a day.

At the completion of 12 weeks of treatment, 70% of patients had moderate or great improvement in PLH and more than 60% of patients showed improvement at all of the hyperhidrosis sites. Two-third of patients presented improvement in quality of life (QOL). QOL was much better in 9 (30.0%), a little better in 11 (36.6%), and the same in 10 patients (33.3%). Dry mouth was the most common side-effect (76.6%). Using 5 mg of oxybutynin per day, 66.6% of patients either did not present dry mouth or only presented it mildly, which encouraged the patients to continue with the treatment. Using 10 mg/d, this symptom increased but was tolerated well. Other side-effects reported were headache (10%) and urinary retention (6.6%); however, they were not significant enough to lead to discontinuation of treatment.

Comment: Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Hyperhidrosis
may be primary or secondary to medications or general medical conditions. Primary hyperhidrosis has an estimated prevalence of nearly 3% of the population. Topical therapy (20% aluminum chloride solution, 15% aluminum chloride in 2-4% salicylic acid gel, and 0.5%, 1%, 2% glycopyrrolate) is generally considered first-line treatment for most cases of focal hyperhidrosis. Other topical agents such as glutaraldehyde, formaldehyde, and tannic acid are seldom used today due to irritancy, skin discoloration, and the availability of better alternatives. For those who fail such treatment, other options available are iontophoresis, botulinum toxin A (BTX-A) injections and surgical or video-assisted endoscopic thoracic sympathectomy. But all these modalities have their limitations.

Only limited data are available regarding the use of oral medications in the management of hyperhidrosis. The various drugs tried include anti-cholinergic drugs: glycopyrrolate (1-2 mg, once/twice daily), oxybutynin (5-15 mg/day) and tolterodine (4 mg/day), and alpha-2-agonists: clonidine (0.6-1.2 mg/d).

Oxybutynin is primarily indicated for urge incontinence where it is used in higher dosage (15 mg/d) and hence leading to a greater incidence of side-effects in these patients. When used in low and progressively increasing doses, it is found to be highly effective for hyperhidrosis with minimum side-effects. There was improvement in hyperhidrosis at all the sites in two-third of the patients. Potential side-effects of oral anti-cholinergics include dry mouth, constipation, nausea, blurred vision, urinary retention, drowsiness, and dizziness. The side effects of oxybutynin are mild as compared to other anti-cholinergics. In this study also, the side-effects were mild and well tolerated by the patients. Because of its rapid resorption (Tmax <1 hour), oxybutynin would also be suitable for use ‘on demand,’ for example, in specific social situations that provoke hyperhidrosis. It is contraindicated in patients with urinary retention, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, gastroesophageal reflux disease, uncontrolled narrow-angle glaucoma and also in those with hypersensitivity to the drug substance. Limitation of the study is that there was no follow up of the patients after the drug was stopped. Treatment of plantar hyperhidrosis is challenging with each therapeutic modality having its own merits and demerits. Treatment of PLH with oxybutynin is a good alternative in patients failing on topical treatment and not willing for i ontophoresis or BTX-A. It has been found to be effective with a minimum of side-effects.


Pemphigus vulgaris (PV) is an autoimmune mucocutaneous blistering disorder. The first-line treatment for patients with PV consists of high-dose glucocorticoids, which have greatly reduced the mortality associated with this disease. This is a retrospective chart review of 23 patients of PV who were treated with methotrexate (MTX) between 2001 and 2012. The primary objective was to evaluate the efficacy of MTX in inducing clinical improvement in PV patients, as indicated by the drug’s steroid-sparing effect and also to determine if it could be effective as a monotherapy in maintaining symptom control.

All the 23 patients included in the study (before the initiation of methotrexate) were treated with prednisone at a mean maximum dose of 71 mg/day (range 20 to 140 mg/day). Thirteen (56.5%) patients had received non-steroidal immunomodulators other than MTX before. The mean dose of prednisone at the time of initiation of MTX was 35 mg/day (range 10 to 70 mg/day). The initial dose of MTX was 7.5 mg weekly, with increases of 5 to 7.5 mg weekly every 2 to 8 weeks depending on the therapeutic response, until a maximum dose of 15 to 25 mg weekly. Folic acid at a dose of 1 mg/day was prescribed. Concomitant treatment with topical glucocorticoids such as clobetasol propionate ointment, dexamethasone oral rinses and intralesional injections of triamcinolone acetonide 20 mg/mL was continued. Symptom control was defined as either complete clearance of skin lesions, or as “minimal disease activity” exemplified by 1 to 2 new lesions every month that could be controlled with topical therapy and that were not considered to cause considerable distress by the patient. In patients achieving symptom control after addition of MTX, prednisone was tapered. Patients who were successfully weaned from prednisone were then put on tapering doses of MTX.

Of the 23 patients included in this study, 2 (8.6%) developed adverse events after initiation of MTX requiring cessation of the drug, while 21 (91.3%) had improvement in blistering and were able to reduce their dose of systemic corticosteroids. Sixteen (69.6%) patients were eventually weaned completely off prednisone, with a mean time from...
initiation of MTX to discontinuation of prednisone of 18 months (range 7-30 months). Five (21.7%) patients experienced a partial steroid-sparing effect requiring a mean maintenance dose of prednisone of 6.75 mg/day. One patient experienced no therapeutic benefit after 2 months of MTX reaching a maximum dose of 25 mg/week. In the 16 patients who were successfully weaned from prednisone, tapering of MTX dose was attempted in 14. Of these 14 patients, the weekly dose of MTX could not be reduced without resulting in a flare of disease in 3 patients, MTX was reduced to 8.75 mg/week (range 5 to 15 mg/week) in 8 patients, and 3 patients were eventually completely tapered from MTX. Of the 3 patients who were completely tapered off MTX, 2 remained in remission for a duration of 3 and 7 months, and the third was in remission lasting for 26 months.

These results were largely unchanged when compared with the subgroup of patients who had previously received other systemic immunomodulators.

Comment: High-dose systemic steroids are considered the first-line of treatment for PV. However, the appreciable morbidity associated with systemic glucocorticoids has resulted in the use of other immunosuppressive drugs like azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, and methotrexate. In addition, dapsone, tetracyclines, plasmapheresis, intravenous immunoglobulin (IVIg), and rituximab have been used successfully. Although good results have been reported with biological agents, their high cost is a major limiting factor.

In this study, steroid dose could be reduced in 91% patients and in 69.6%, prednisone was completely tapered. MTX is a safe and efficacious treatment for patients with PV and should be included in the adjuvant therapy armamentarium. Another advantage is that it is a relatively cheap and easily accessible drug with which dermatologists have a vast experience. MTX generally has a delayed beneficial effect on oral lesions, whereas the cutaneous lesions usually respond more rapidly. In patients with severe to moderately severe PV, once the initial disease has been brought under control using high doses of systemic corticosteroids, MTX may be useful in maintaining that control, while allowing a lowering of the corticosteroid dose. It may even be successful in controlling the disease as a monotherapy, but it usually does not lead to complete prolonged remission of the disease.

Most of the studies showing efficacy of MTX in PV have been retrospective case series. Previous studies also suggest that a significant number of patients show clinical improvement with MTX and the drug has steroid-sparing effects. Further prolonged, placebo-controlled or multiple-arm prospective clinical trials are needed in order to further assess the role of MTX in the treatment of PV.


Melasma is a highly prevalent, chronic pigmentary disorder. Tranexamic acid (TA) is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. This article reviews the rationale use and safety profile of TA as an adjuvant treatment in melasma.

TA has been tried in the treatment of melasma in the oral, topical, and intradermal injection formulation. Eight studies using oral TA (0.5-1.5 g/day) in the treatment of melasma were reviewed. The response to therapy was evaluated after 4-10 weeks of starting the drug. It was concluded that the usual effective dose of TA in melasma can be 250 mg 2-3 times daily, which is much lower than the dose used to reduce excessive bleeding. Clinical response was observed after a period of at least 1 month. Side-effects in the form of gastrointestinal upset and a decrease in the amount of menses were found in a minority of patients (3-4%). No change was found in the coagulation parameters. Recurrence of melasma was seen after stopping treatment in a few patients. It was also found that the duration of the therapy and not the higher dose made the treatment regime more effective.

Since systemic TA has potential side-effects, topical TA has been tried in melasma. Available data in literature on the efficacy of topical TA is scarce, and results are conflicting. Some studies suggest that melasma improves in significant number of patients with topical 2% TA emulsion when applied for 5-18 weeks and no side-effects were observed. While another study showed that topical 5% TA when used for a 12-week period caused more irritation to the applied area without any extra benefit. Recently, topical TA in liposome formulation has been developed to reduce irritation.

One study has reported on the efficacy of intradermal injections of TA. The study showed that 85 patients who completed weekly intradermal injections of TA, 0.05 ml TA (4 mg/mL) in the melasma lesion at
1 cm intervals for 12 weeks had significant decrease in the melasma area and severity index (MASI) from 8 weeks onward (8 rated good, 65 rated fair results). No significant side-effect was noted.

Comment: The pathogenesis of melasma is multifactorial; genetic predisposition, UV light exposure and hormonal influences being the major etiologic factors.

TA is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. It acts by attaching to the lysine-binding sites of plasmin and plasminogen. It inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, thus suppresses the production of prostaglandins (PGs) and UV-induced melanogenesis, through the suppression of the epidermal plasmin activity. Lesser free arachidonic acids and depleted production of PGs reduces the melanocyte tyrosinase activity. This might be the mechanism for the effect of TA on melasma and improvement of post-inflammatory hyperpigmentation. Besides, it also reverses melasma-related dermal changes, such as vessel proliferation and increased number of mast cell.

In the majority of studies showing the efficacy of TA in melasma, the drug has been given orally. Although systemic TA has been reported to be safe for the treatment of melasma, the risk-benefit study must be done on a larger scale. The primary side-effects noted with its use are gastrointestinal complaints (nausea, diarrhea, and abdominal pain). There are also reports of serious complications such as deep venous thrombosis, pulmonary embolism, cerebral artery thrombosis and embolism, and coronary artery thromboembolism.

There is limited published literature on the role of topical TA and intradermal TA injections in melasma. Topical TA may cause irritation and allergy. Therefore, novel topical TA liposome formulations have been developed, but they are not yet commercially available. By injecting TA intradermally, it may be possible to treat the dermal and mixed-type melasma. Intrallesional microinjection of TA appears to be a potentially new and promising therapeutic tool that can be easily performed in outpatient settings, with relatively rapid results and without significant side-effects.

Although many agents are available in the therapeutic options of melasma, its management is still challenging and recurrences are common. TA can prove to be a useful adjunct in the treatment of this difficult to manage disorder of hyperpigmentation. It may also have some synergistic activity when used in combination with the other treatment modalities. But, like other available treatment options, it is not uniformly effective in all the cases. It leads to improvement in pigmentation in many patients, complete clearance in few, and recurrences can occur on stopping the treatment.


Chronic idiopathic or spontaneous urticaria (CU) affects around 0.1% of the population and can be highly distressing. It is defined by the presence of daily or almost daily symptoms for more than 6 weeks. Omalizumab is a monoclonal anti-IgE antibody approved for the treatment of severe allergic asthma and is also being tried in CU. This is a retrospective case series of 15 patients with CU treated with omalizumab. Omalizumab was administered at a dose of 150-300 mg subcutaneously every 2-4 weeks; the dosage used was adjusted according to total weight and serum IgE levels. Improvement was assessed after 3 and 6 months of treatment. Complete response was defined as symptom disappearance that could be followed by discontinuation of anti-histamines, and partial response as symptom improvement, but with symptom worsening when attempting to discontinue anti-histamines. After 3 months of treatment, 12 patients responded, with partial response in 9 and complete response in 3. At 6 months, 8 of 10 patients continuing on omalizumab had a complete response and 2 had a partial response. In patients discontinuing the drug, symptoms recurred after 5 weeks without treatment. Only 2 patients reported dizziness or nausea after the injections.

Comments: The chronic types of urticaria are divided into physical urticaria (cold, delayed pressure, vibratory urticaria, and urticaria factitia), other urticaria types (aquagenic, cholinergic, contact urticaria, and exercise-induced urticaria/anaphylaxis), and spontaneous urticaria. Chronic spontaneous urticarias may be idiopathic (55%) or autoimmune (45%) as defined by the presence of the immunoglobulin IgG against the alpha subunit of the high affinity IgE receptor, or IgG anti-IgE antibodies.

The first-line drugs for the treatment of CU are second generation H1 anti-histamines. In non-responders,
Prashar and Yadav

Current best evidence from dermatology literature

the dose of the anti-histamine can be increased up to four-fold of the recommended dose or sedating H1 anti-histamine/H2 anti-histamine may be added. The second-line therapies are doxepin, leukotriene receptor antagonist, corticosteroid (short-term only), dapsone, chloroquine, hydroxychloroquine, and sulfasalazine. The third-line treatments include methotrexate, cyclosporine, mycophenolate mofetil, omalizumab, autologous serum therapy, intravenous immunoglobulin, and plasmapheresis.

Omalizumab is a recombinant humanized anti-IgE-IgG monoclonal antibody approved for the treatment of moderate to severe allergic asthma. It blocks the high-affinity Fc receptor of IgE and also reduces the expression of FcεRI on circulating basophils and mast cells, thus reducing their activation and histamine release. In addition to the anti-IgE mechanisms, it also induces eosinophil apoptosis, downregulates inflammatory cytokines IL-2, IL-4, IL-13, and TNF-alpha. This explains the successful results of omalizumab in CU patients even with low levels of serum IgE.

Omalizumab has been shown to be effective in chronic autoimmune urticaria, chronic idiopathic urticaria and various urticaria subtypes such as cholinergic, heat, cold, solar, and delayed pressure urticaria. It is used in doses of 150 mg or 300 mg subcutaneously every second or fourth week, depending on the weight and serum IgE levels. It has been found to be effective in restoring the patient’s quality of life and in reducing the urticaria activity score. Few or no side-effects have been reported with omalizumab therapy. The most frequent adverse events noted are nausea, flu-like symptoms, diarrhea, nasopharyngitis, upper respiratory infection, and headache. Anaphylaxis has very rarely been reported (<0.1%). Omalizumab is an excellent treatment choice for severe treatment-refractory urticaria. It allows for a significant reduction in the dose of anti-histamines, systemic steroids, and other immunosuppressives in patients with CU, thus minimizing their side-effects. The drawbacks with this therapy are the high cost, not uniformly effective in all patients, prolonged treatment, and risk of recurrence on stopping the treatment. Further studies should be performed to confirm its efficacy in urticaria refractory to the conventional treatment.

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Are dermatologists familiar with acronyms?

Sir,
Acronyms were initially introduced during the early 20th century, which places them among the relatively new linguistic phenomena with wide spectrum of definitions. The purpose of this study is to analyze the current knowledge of Serbian dermatologists regarding the recognition of acronyms and assessment of familiarity with selected acronyms among practicing dermatologists with the practice experience of various duration.

The anonymous inquiry questionnaire containing poetic letter with 10 hidden acronyms [Appendix 1] has been delivered to 52 certified practicing dermatologists. The final mixture of acronyms hidden in the text included 54-year-old up to 2-year-old acronym. Only 26.7% recognized more than 50% of the hidden acronyms [Figure 1]. Two groups emerged: The “poor” and “good” acronym knowledge group of dermatologists [Table 1]. Dermatologists in the “poor” knowledge group were significantly older with the higher mean age ($P < 0.05$), majority of participants (85.7%) in this group had more than 10 years of practice. Conversely, up to 79.2% dermatologists in the “good” knowledge group were younger specialists who started to practice within the past decade ($P < 0.001$). Moreover, their own perception of fluency in speaking English ($P < 0.05$) is greater. Gender, type of practice (public vs. private) and the presence or absence of English language education, did not significantly differ between “good” and “poor” acronym knowledge group.

Specific type of acronym was significant for the recognition process so in the "good" knowledge group, terms SAPHO, CHILD, LAMB, DRESS, and KID were significantly more frequently detected by dermatologists. The most frequently detected acronyms in both groups were LEOPARD and SAPHO, respectively.

According to the MedLine and PubMed database search, more than 90 abbreviations were recorded in dermatology regarding the naming of dermatological diseases and syndromes (e.g. SSSS, AD, DLE). Some

### Table 1: Characteristics of dermatovenereologists according to the number of recognized acronyms

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1-3 acronyms (group I)</th>
<th>4-7 acronyms (group II)</th>
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<td>Own perceptions of knowledge in english</td>
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<tr>
<td>Poor</td>
<td>8</td>
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<tr>
<td>Good</td>
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<td>11</td>
<td>45.8</td>
</tr>
<tr>
<td>Excellent</td>
<td>1</td>
<td>8</td>
<td>33.3</td>
</tr>
</tbody>
</table>

*P value according $\chi^2$ test, **P value according $t$ test, SD: Standard deviation

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of the commonly used acronyms describing diseases or syndromes in dermatology are (in alphabetical order) AGEP, BIDS, CHILD, CLOVE, COIF, CREST, DRESS, EMPACT, HATS, ILVEN, KID, LAMB, LEOPARD, MIDAS, NAME, PAN, PAPA, PHACES, POEMS, REM, SACRAL, SAPHO, SDRIFE, TEN, and WILD. The first acronym used in dermatology, TEN appeared only 13 years after the official acceptance of the exact acronym definition, and the rise of acronyms in naming of dermatoses and syndromes continued during the past 6 decades.[1]

Since, the dermatology is visual i.e. descriptive medical specialty one could expect that the theory of visual word recognition would have the greatest impact on identification and memorization of acronyms.[2] This might well be supported by study on acronym “superiority effect” which presents that familiarity of a word (i.e., with pre-existing lexical representation) has even superior effect on recognition and memory than orthographic regularity (effective spelling of the letter string) when it comes to visual word recognition.[3]

The acronymophyllia which appeared in other medical fields could have been easily avoided in dermatology by using three simple rules when creating one: (1) the acronym must have at least three letters and be easily pronounceable, (2) it has to make the communication easier, (3) and to be more readily recognized by the reader compared to the original phrase[4] adding the familiarity as the most important characteristic. All acronyms elected in the study obey the proposed rules: Surprisingly well-recognized acronym SAPHO could only be explained by Serbian-Greek historical connections and hence familiarity with Greek goddess Sapho.

Since, its cumbersome to memorize all the acronyms and syndrome names (NAME, LAMB, LEOPARD, Carney syndrome) that refer to almost the same skin lesions: Lentigines and/or ephelides and various benign tumors, all of them being rare, only the oldest acronym LEOPARD was highly recognizable, which emphasizes the significance of the clinical endpoint.[5]

The duration of acronym usage and interpretation in dermatology appeared to be important factor in recognition of “older” acronyms but only in case of a half-century old mnemonic words which holds primarily for LEOPARD. Similarly, there was complete ignorance of the 2 year old term WILD.

Influence of fluency in speaking English on acronym recognition is evidenced in this survey. Word leopard have the same written and pronounced version in Serbian unlike the “animal” lamb, which remained unrecognized by poor English speakers.

In conclusion, the strongest evidence stands for positive causality between the amount of time spent on acronym usage in dermatology and the extent of visual word recognition, with significant positive influence of the recently gained knowledge through board exam (not more than 10 years of practice), younger age of practicing dermatologist and fluency in English.

ACKNOWLEDGMENT

This study was supported by the Ministry of Science and
Appendix 1: Poetic letter with hidden acronyms

Dear Papa,

I went to the Zoo with our new teacher. Her name is Sapho, she is Greek. She took her own child, Alexander, with us. We saw many wild animals, like tigers, wolves, lions and a leopard, but most of all I liked a pretty little lamb. I was wearing the red dress you’ve bought me for my birthday.

Zoo ticket was ten Euros.

All my love to mom and you,

Your kid Mary


MARKOVIĆ MILICA, IVANOVIĆ BRANISLAV, BJЕKIĆ MILAN, SIPETIC SANDRA

City Institute for Skin and Venereal Diseases, Belgrade, Faculty of Philology, Belgrade University, Belgrade, Institute of Epidemiology, School of Medicine, Belgrade, Serbia

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REFERENCES


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| 10.4103/0378-6323.120756 |
Familial congenital generalized hypertrichosis

Sir,

Hypertrichosis is defined as an abnormal hair growth resulting in an increase in body hair beyond the normal variation for a patient's reference group; excluding androgen-induced hair growth. This should be differentiated from hirsutism, which is increased hair growth in androgen dependent areas. It is usually a cosmetic problem, but may be associated with an underlying disorder that requires further investigation. It has been classified into congenital and acquired with further subdivision into generalized or localized hypertrichosis. We present a rare case of familial congenital generalized hypertrichosis, which on literature search has been reported in very few families worldwide.

An 18-year-old girl, presented with profuse hair growth over face, arms, legs and back since birth. Her thelarche and menarche were normal and menstrual cycles were regular with normal flow. There was no history of acne, weight gain or voice change. Both her mother and maternal grandmother had a similar history of extensive body hair while her two sisters were normal. On examination, she was phenotypically female with a body mass index of 26. Extensive, soft, black terminal hair, 3-4 cm long was present on the face (shaved), arms, back, buttocks and lower limbs [Figures 1 and 2]. Adult sexual hair was seen in axilla and pubic area.

Hair on chest and abdomen was sparse. There was no hair on palms, soles and mucosal surfaces. Both breasts were normal and there was no clitoromegaly. There were no associated dental anomalies, facial dysmorphism or gingival hyperplasia. Hormone levels were within range (Luteinizing Hormone 4 IU/L, Follicle Stimulating Hormone 3.5 IU/L, Estradiol 54 pg/ml, Thyroid-Stimulating Hormone 2.2 µIU/ml and testosterone 0.9 ng/ml). Uterus and ovaries were normal on ultrasound. A diagnosis of congenital generalized familial hypertrichosis was made. Patient was counseled and referred for full body laser treatment. However as she could not afford the treatment, she continued with shaving and waxing.

Congenital generalized hypertrichosis has terminal hair with typical phenotypic characteristics as described in our patient and has an autosomal or X-linked dominant pattern of inheritance, which has been linked to chromosome x24-q27.1. Various mechanisms of hypertrichosis have been described; such as prolonged anagen phase of hair follicles, increased hair follicle density and abnormal vellus to terminal switch mechanism in normal vellus hair bearing areas. Terminal hair is medullated, wider than the inner root sheath of the follicle that produces them and the follicle penetrates into the reticular dermis. It can be easily differentiated from the softer

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**Net Letter**

Familial congenital generalized hypertrichosis

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Non-medullated lanugo and non-pigmented variably medullated vellus hair.[4] Other forms of congenital syndromes with primary generalized hypertrichosis are congenital hypertrichosis lanuginose (CHL), gingival fibromatosis with hypertrichosis, Cantu's syndrome and hypertrichosis, pigmented retinopathy and facial anomalies syndrome.[2] In CHL, the hair distribution is similar to generalized hypertrichosis except that there is uniform overgrowth of soft lanugo hair with or without facial dysmorphisms (Ambras syndrome).[5]

No single method of hair removal is appropriate for all body locations or patients and the one adopted will depend on the character, area and amount of hair growth as well as on the age of patient and their personal preference. Techniques of hair removal can be temporary or permanent.[2] Temporary methods can be depilatory such as shaving, cutting or chemical depilators or epilatory such as plucking, waxing or tweezing.[2] Patient continued to use these temporary methods. Permanent methods of hair removal include electrolysis, thermolysis or laser treatment. The longer wavelength Nd: YAG laser is considered safest in treating darker skin phototypes.[6]

Reporting such rare syndromes not only adds to the database, but pooled data analysis may give us a better insight into patterns of inheritance, epidemiology and associated symptoms.

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Sir,
Cutaneous side-effects of heparins are well-known. Among them, nodule development is uncommon. Usually, these nodules reveal calcinosis cutis on histological examination.

A 66-year-old woman presented with pruriginous lesions on her abdomen, 25 days after initiating oral acenocoumarol and subcutaneous enoxaparin for a pulmonary thromboembolism. On physical examination, multiple tender, poorly delimited, subcutaneous nodules at enoxaparin injection area were evident [Figure 1]. A biopsy and several complementary studies were performed. Hemogram, erythrocyte sedimentation rate, serum chemistry including alpha-1-antitrypsin, lipase, tryptase, angiotensin I-converting enzyme, rheumatoid factor, thyroid hormone function, autoimmune studies, urinalysis, chest X-ray and purified protein derivative test were all normal, except for slight eosinophilia with normal white cell count. Cutaneous biopsy showed a mainly septal panniculitis [Figure 2]. The inflammatory infiltrate was predominantly composed of eosinophils, together with few lymphocytes and histiocytes, within the thickened septa and lobules [Figure 3]. In the dermis, scant perivascular and interstitial inflammatory cell infiltrate composed predominantly of eosinophils was evident. Mild overlying spongiosis was also identified. A diagnosis of cutaneous drug reaction with eosinophilic panniculitis induced by heparin was made. Enoxaparin injections were discontinued, which resulted in cutaneous improvement. A positive patch test to enoxaparin confirmed this diagnosis.

The incidence of skin lesions induced by subcutaneous heparin is unknown. Urticaria, angioedema, ecchymosis, cutaneous necrosis, cutaneous induration and eczema-like lesions have been reported secondary to heparin administration. Delayed-type hypersensitivity reactions appear to be the most common mechanism to develop these cutaneous lesions. The presence of nodules or panniculitis caused by heparin has rarely been described. The majority of these patients presented with calcinosis cutis or subcutis on histological examination and only one case of eosinophilic panniculitis was reported. Most patients with nodules were receiving treatment with calcium non-fractionated heparins or low molecular weight heparins (LMWH) containing calcium salts. On the other hand, patients with calcinosis cutis following subcutaneous heparin injection usually

Figure 1: Subcutaneous nodules in areas of heparin injection (abdomen)

Figure 2: (a and b) Cutaneous drug reaction with eosinophilic panniculitis induced by heparin. Low power view showing inflammatory infiltrate in the upper dermis, thickened septa and lobules (H and E, ×40)

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suffered from vitamin D, parathyroid hormone or calcium-phosphate disturbances.[2] Nodules induced by sodium LMWH have also been found. Funt et al. observed nodules in 14 of 426 cancer patients following dalteparin (heparin with sodium salts) injection. These authors described the radiological characteristics of these nodules, but histological studies were not performed.[3]

Regarding to acenocoumarol, the absence of reported cases of panniculitis caused by this drug as well as the involution of cutaneous lesions despite continuing with this treatment, helped us to exclude acenocoumarol as a possible cause of the lesions of our patient.

Eosinophilic panniculitis is a rare form of panniculitis characterized by septal and lobular involvement with eosinophilic infiltration. It is believed to be a reactive process that has been associated with a variety of systemic conditions such as gnathostomiasis, leukocytoclastic vasculitis and erythema nodosum.[4] In rare instances, eosinophilic panniculitis has been observed as a local phenomenon induced by subcutaneous or intramuscular drug injections including apomorphine, specific immunotherapy, benzathine penicillin and calcium heparin.[1,5] Delayed-type hypersensitivity reactions have also been considered as the cause of these reactions.[5]

CONCLUSION

To the best of our knowledge, this is the first case of eosinophilic panniculitis induced by administration of LMWH containing sodium salts.

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Sir,

De Sanctis-Cacchione syndrome (DSC) (MIM #278800) is a rare autosomal recessive disorder with a gene map locus of 10q11, originally described as “xerodermic idiocy.”[1] DSC is characterized by cutaneous photosensitivity, microcephaly, mental retardation, short stature, hypogonadism, spasticity, peripheral neuropathy and sensorineural deafness.[2] In most of the cases in the literature, hypogonadism has been described, but we report a case of DSC with intact gonadal functions.

A 10-year-old boy presented with multiple episodes of myoclonic seizures and progressive, rapid loss of milestones, cognition, vision and hearing for the past 6 months. There was a history of persistent drooling of saliva, nasal regurgitation of feeds with episodes of choking and coughing with attempted solid feeds. The child was confined to bed and gave no indications for thirst, hunger, bladder or bowel needs. There was no response to auditory and visual stimuli. Past history suggested dry and scaly skin and photosensitivity (since infancy) and developmental delay (developmental quotient 0.33; revised Denver Developmental Scale II). The child was a third in birth order, product of a third degree consanguineous marriage with high maternal (40 years) and paternal (45 years) age, born at term with an uneventful neonatal period. Other siblings were unaffected and there was no family history of photosensitivity, seizures or mental retardation. On examination, the child was emaciated with a weight of 15 kg (<3rd percentile), length of 122 cm (<3rd percentile), body mass index of 10.1 (<3rd centile) and head circumference of 45 cm (<3rd percentile). Facial features were suggestive of “Old man look” with an elongated face, micrognathia, pinched nose and crowded caries teeth. The skin lesions were noted over the face, neck, upper chest and exposed parts of limbs and consisted of scaling, erythema, crusting with patches of hyperpigmentation [Figure 1]. He had fixed contractures of the ankle, knee, elbow and wrist joints [Figure 2]. The genitals, including the penis and testes, were normal with a stretched penile length of 4.5 cm (−2.5 standard deviation = 3.7 cm) and Tanner’s sexual maturity rating (SMR) of stage 2. Examination of the central nervous system revealed that the child had spontaneous eye opening without focusing, motor response of localization to pain and incomprehensible vocal response. Fundus examination revealed the presence of salt and pepper retinopathy. Brainstem evoked auditory response revealed severe sensory-neural hearing loss. Pharyngeal reflex (gag reflex) was weak suggestive of bulbar involvement. On examination, 3rd, 4th, 5th, 6th, 7th and 12th cranial nerves were normal. Motor system examination showed a decrease in muscle bulk, increased tone, reduced power (1/5) and contractures at knee, ankle, elbow and wrist joints. The elicitation of deep tendon reflexes were masked by fixed contractures. There were no abnormal movements and no cerebellar or meningeal signs. Examination of the abdominal, respiratory and cardiovascular systems revealed no other abnormalities. Laboratory investigations showed a normal hemoglobin (Hb 12.1 g/dl), serum creatinine (0.8 g/dl), serum albumin (3.5 g/dl), alanine aminotransferase (24 IU/L) and alkaline phosphatase (120 IU/L). Skeletal survey showed a bone age of 11-12 years. Contrast-enhanced computed tomography (brain) revealed dilated lateral ventricles, atrophy of cerebral and cerebellar cortex and hydrocephalus (ex-vacuo) with no intracranial calcifications [Figures 3 and 4]. Nerve conduction velocity of upper and lower limb suggested axonal neuropathy. Electromyography revealed a decline in motor unit recruitment and other nonspecific changes. Based on the constellation of above features, a diagnosis of DSC was established.

The child was advised protection from sun exposure by the use of protective clothing, eyeglasses, broad spectrum sunscreens containing para-aminobenzoic acid esters and skin emollients. Seizures were controlled with sodium valproate (25 mg/kg) and lamotrigine mg/kg (2.5 mg/kg/day). Physiotherapy was initiated to prevent the worsening of contractures. Child was on regular follow-up for next 6 months. Seizures were controlled with no further progression of neurological illness.
Xeroderma pigmentosa (XP) results from defects in the excision repair of ultraviolet (UV) induced deoxyribonucleic acid (DNA) damage. Defects in nucleotide excision repair (NER) results in inherited neurocutaneous syndromes such as XP, Cockayne syndrome and trichothiodystrophy. There is a complex relationship between NER mutations and clinical features. Seven xeroderma pigmentosum genes, XPA through XPG, have been identified. Conversely, different mutations in one gene can lead to different clinical disorders with variation in systemic involvement.[2,3] The gene locus implicated in DSC is ERCC6, which is located at 10q11, which is also called Cockayne syndrome-B gene.[4]

Among the variants of XP, patients with DSC have the greatest UV sensitivity and the poorest DNA repair. The neurological manifestations in XP have been hypothesized to be secondary to defective DNA repair in the neuronal cells resulting in neuronal death or dysfunction. Although neurological symptoms appear in the first two decades of life, late presentation in adults has also been reported.[5] The common neurological manifestations of DSC are progressive neurological deterioration, peripheral neuropathy and sensorineural deafness observed in 18% of cases.[6] Other manifestations include microcephaly, choreoathetosis, cerebellar and extra pyramidal syndromes.[7] The late onset of neurological complaints and the relative preservation of gonads and sexual maturity in our case depict sparing of cells from UV induced damage. Early intervention and appropriate protection from sunlight started early in the illness could have a significant impact in delaying the onset of neurological symptoms. There are very few cases reported with complete manifestations of this syndrome. However, many patients have one or more of its neurological features. The features that favored a diagnosis of DSC in our case were mental retardation, microcephaly, cutaneous photosensitivity, stunting, spasticity, contractures, sensorineural deafness and peripheral neuropathy. However, unlike the classical
DSC, our child had normal gonads and sexual maturity staging at the time of presentation. In the absence of cataract, optic atrophy, skeletal dysplasia and basal ganglia calcifications, Cockayne syndrome was ruled out.

Diagnosis of DSC is mainly based on clinical features. Chromosomal breakage studies, complementation studies and gene sequencing to identify the specific gene complementation group are supportive. The mainstay of treatment is adequate sun-protection and regular follow up for the early detection of cutaneous malignancies. This condition is not curable and lesser than 40% patients with severe manifestations survive beyond the second decade of life. A multidisciplinary approach, involving a Neurologist and an Ophthalmologist, is required to deal with the associated conditions. A novel approach to photo protection is to repair DNA damage after UV exposure by the delivery of a DNA repair enzyme into the skin by means of specially engineered liposomes. T4 endonuclease V has been shown to repair cyclobutane pyrimidine dimers resulting from DNA damage.[8] Gene therapy for XP is still in a theoretical and experimental stage. The earlier onset of disease is associated with a poorer prognosis. Parental counseling plays a significant role in the reduction of future recurrence as prenatal diagnosis is possible by amniocentesis or chorionic villous sampling.

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Erythematous indurated plaque lesions on the breast

A 50-year-old female patient, who had retraction of the right nipple for 2 years and erythema in the same breast for 2 months, was referred to our clinic. Mammography and breast ultrasonography performed at the time of onset of nipple retraction were normal. Dermatological examination revealed three erythematous, mildly indurated plaque lesions on the right breast, one of which involved the areola [Figure 1]. The nipple was retracted. The patient had no subjective complaints. The right axillary examination detected several lymphadenopathies, as confirmed by ultrasonography.

The histopathological examination of the skin biopsy revealed islands of tumor cells in the dermal lymphatics [Figure 2]. These infiltrations consisted of round-shaped atypical cells with vesiculated nuclei and marked nucleoli. In immunohistochemical studies, strong positive staining by low-molecular weight keratin (LMWCK) and epithelial membrane antigen (EMA) and non-specific staining by vimentin have been detected.

WHAT IS YOUR DIAGNOSIS?

Figure 1: Three erythematous plaques on the right breast, one involving the areola

Figure 2: Tumor islands consisted of atypical epithelium cells in the lymphatics (H and E, ×200)

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Net Quiz

**Answer: Carcinoma erysipeloides**

**DISCUSSION**

The rate of skin metastasis in internal malignancies varies from 0.7 to 10%. The skin metastases may occur as a result of lymphogenous, hematogenous spread, or direct invasion of surrounding tissue by tumor cells. Skin metastases usually occur as a finding of the spread or the recurrence of internal malignancies; however, they may rarely be an initial finding of an undetected malignancy.

Carcinoma erysipeloides (CE) is a rare cutaneous metastasis, which results from the lymphatic spread of an inflammatory carcinoma. While it is mostly related to breast cancer, it may also result from other tumors. In our case, a solid mass lesion was also detected in the right breast, and the biopsy performed at the General Surgery Department was reported as invasive ductal carcinoma.

In the differential diagnosis of CE, erysipelas, cellulitis, radiation dermatitis, and contact dermatitis should be considered. The exact diagnosis of CE is made by histopathology. The dermal lymphatic invasion is considered as the characteristic feature of CE.

Other than breast cancer, nipple retraction may occur due to periductal mastitis, ductal ectasia, tuberculosis, sarcoidosis, fungal infections, and granulomatous inflammatory diseases, including Wegener’s granulomatosis and idiopathic granulomatosis lobular mastitis. In our case, nipple retraction began 2 years ago, and the laboratory examinations performed at that time revealed no pathology. Therefore, nipple retraction was not considered to be associated with breast cancer.

In general, CE develops several months or years after the diagnosis of primary carcinoma. CE is an indicator of poor prognosis, and patients often die within few months of its diagnosis. CE developing as an initial sign of undiagnosed tumor is rare. Interestingly, in our patient, CE was diagnosed before the diagnosis of breast cancer.

In cases of CE, treatment of primary tumor is sufficient. Surgical treatment is not recommended. Systemic chemotherapy and hormonal therapies alone or in combination with radiotherapy represent the basic treatment options. We also referred our patient to the general surgery and oncology departments for planning the treatment of primary tumor.

**CONCLUSION**

While the skin metastases generally occur after the diagnosis of primary tumor, they may also develop prior to diagnosis. The skin invasions can be clinically confused with other disorders. This may result in delayed diagnosis of the malignancy and decrease in survival. Our case demonstrated the importance of non-specific skin lesions such as erythema in diagnosis of breast cancer. Therefore, the dermatologists should be careful with respect to cutaneous metastases, even if the patient’s medical history does not include malignancy.

**REFERENCES**

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