Case Report

Ductal invasive carcinoma arising within atypical microglandular adenosis in a patient with BRCA-1 mutation: A case report

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Abstract

Microglandular adenosis (MGA) of the breast is a benign lesion that may mimic invasive carcinoma and which has been proposed to be a potential precursor of triple-negative breast carcinoma. It differs from other types of adenosis due to the infiltrative growth pattern and the absence of a myoepithelial layer, crucial hallmarks of benign breast lesions, so it may be easily confused for an invasive carcinoma [1]. Radiological, pathological and genetic studies have reported the potential role of this lesion as a precursor of a significant number of triple-negative breast carcinomas, suggesting that this role could be underestimated because the rapid growth of a high grade triple-negative carcinoma could mask this "precursor lesion" [1–3]. Germline mutations in BRCA-1 (tumor suppressor gene involved in cellular response to DNA damage) are known to confer a high risk of breast and ovarian cancer, with a cumulative risk of developing a breast cancer by age 70 years of about 55–65% [4,5]; in studies investigating the incidence of BRCA-1 mutations in unselected series of triple-negative breast carcinoma, approx. 15% of patients show BRCA-1 mutations [5–7]. In BRCA-1 mutation carriers, breast malignancy is likely to present as an invasive cancer of no special type (NST) or medullary-type, with high histologic grade and high Ki-67 index, a basal-like phenotype (expression of EGFr and luminal cytokeratins such as CK 8/18, negative for high molecular weight cytokeratins such as CK 5/6), with a crucial role played by p53 mutation as “driver mutation” in the multistep model of carcinization. When an invasive carcinoma arises in a background of MGA, it is possible to identify a clear multistep transition from conventional MGA to atypical MGA (AMGA), Ductal Carcinoma In Situ (DCIS) arising within AMGA and invasive carcinoma. This is the first histological case report of an invasive carcinoma arising within MGA and AMGA in a patient carrying a germline BRCA-1 mutation, recognized as one of the most important genetic alterations correlated with the development of triple-negative carcinoma.

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1. Introduction

Microglandular adenosis (MGA) is an uncommon, benign breast lesion that may mimic invasive carcinoma and which has been proposed to be a potential precursor of triple-negative breast carcinoma. It differs from other types of adenosis due to the infiltrative growth pattern and the absence of a myoepithelial layer, crucial hallmarks of benign breast lesions, so it may be easily confused for an invasive carcinoma [1]. Radiological, pathological and genetic studies have reported the potential role of this lesion as a precursor of a significant number of triple-negative breast carcinomas, suggesting that this role could be underestimated because the rapid growth of a high grade triple-negative carcinoma could mask this “precursor lesion” [1–3]. Germline mutations in BRCA-1 (tumor suppressor gene involved in cellular response to DNA damage) are known to confer a high risk of breast and ovarian cancer, with a cumulative risk of developing a breast cancer by age 70 years of about 55–65% [4,5]; in studies investigating the incidence of BRCA-1 mutations in unselected series of triple-negative breast carcinoma, approx. 15% of patients show BRCA-1 mutations [5–7]. In BRCA-1 mutation carriers, breast malignancy is likely to present as an invasive cancer of no special type (NST) or medullary-type, with high histologic grade and high Ki-67 index, a basal-like phenotype (expression of EGFr and luminal cytokeratins such as CK 8/18, negative for high molecular weight cytokeratins such as CK 5/6), with a crucial role played by p53 mutation as “driver mutation” in the multistep model of carcinization. When an invasive carcinoma arises in a background of MGA, it is possible to identify a clear multistep transition from conventional MGA to atypical MGA (AMGA), Ductal Carcinoma In Situ (DCIS) arising within AMGA and invasive carcinoma. This is the first histological case report of an invasive carcinoma arising within MGA and AMGA in a patient carrying a germline BRCA-1 mutation, recognized as one of the most important genetic alterations correlated with the development of triple-negative carcinoma.

2. Report of the case

An asymptomatic 43-year-old woman, with a family history strongly suggestive for hereditary breast-ovarian cancer syndrome, was found to carry a germline BRCA-1 c.5062delGTT mutation (the same mutation previously identified in her sister affected by pre-menopausal bilateral breast cancer) and enrolled into the program for hereditary breast cancer risk management [11]. Clinical examination revealed a firm,
dominant mass with no distinct borders of approximately 2 cm in the outer-upper quadrant of the left breast, without palpatory signs of axillary lymph node involvement as well as no spontaneous or provoked nipple discharge. Mammography and ultrasonography confirmed the suspicious nature of the mass and MRI described a 20 mm lesion in the above-mentioned quadrant with undefined borders and a "type-3" enhancement kinetic curve. No clinical and radiological abnormalities were detected in the controlateral breast. Ultrasound-guided biopsy of the lesion was performed in a different hospital leading to a diagnosis of "invasive breast carcinoma with acinic-like features, negative for estrogen and progesterone receptors, negative for HER2 (scored according to the current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines [12]). P53 staining was semiquantitatively assessed in each type of lesion (MGA, AMGA, DCIS and invasive carcinoma), estimating the percentage of positive nuclei as determined by scanning the slide at low power (40×). Bcl-2 was scored according to semiquantitative classification provided by Trerè et al. [22,23]. EGFr membranous staining was considered positive if present in more than 30% of the cells, intermediate between 10 and 30% and negative if less than 10%. The lesion was considered positive for S-100 protein if any cells displayed nuclear and/or cytoplasmic expression. Indeed, to confirm the lack of a myoepithelial cell layer, an immunohistochemical analysis of SMM (smooth muscle myosin) was performed and only cytoplasmatic staining was considered specific [2]. An Alpha-1-Antichymotrypsin (ACT) staining was performed to investigate the possibility of an invasive carcinoma with acinic-like features, previously diagnosed on the core needle biopsy performed in another hospital. Normal suitable breast tissue was adopted as internal control, in agreement with the AIOM/SIAPEC 2010-ASCO/CAP 2010 guidelines [24,25].

4. Pathological findings

4.1. Macroscopic

The mastectomy specimen was a 21 × 15 × 4 cm portion of fatty breast tissue without skin and nipple ("nipple-sparing mastectomy"), displaying a 4 × 3 cm solution of continuity because of the previous removal of the retroareolar disk. The specimen showed a 2 cm neoplastic nodule located in the outer upper quadrant.

4.2. Microscopic

Microscopic examination of the specimen showed a high grade (G3 for Elston-Ellis) invasive carcinoma of no special type (NST) with a small percentage of conventional type, solid, high-grade in situ carcinoma (DCIS grade 3 — DIN3). The invasive component displayed a heterogeneous growth pattern (cords, nests and tubules), with an intense desmoplastic stromal reaction, scanty aspects of matrix deposition and low intra/peritumoral lymphocytic infiltrate (stromal TILs = 10%).
4.3. Immunohistochemical findings

Immunohistochemical results for invasive carcinoma are listed in Table 1. Atypical microglandular adenosis (AMGA) was negative for smooth muscle myosin (confirming absence of a myoepithelial layer, see Fig. 8), positive for EGFr, S-100 and p53, with a Ki-67 of 15%. p53 and Ki-67 showed a trend in increasing positivity from MGA and AMGA to DCIS arising in AMGA and finally to invasive carcinoma (Figs. 5, 6 and 7), confirming that p53 and Ki-67 expression, in addition to a careful morphological examination, allows to better define areas of transition from atypical microglandular adenosis (AMGA) to infiltrative carcinoma, as previously noted by Ibrahim Khalifeh et al. [26]. Atypical microglandular adenosis (AMGA) and invasive carcinoma were negative for alpha-1-antichymotrypsin, in contrast with a diagnosis of invasive carcinoma with acinic-like features.

5. Comment and conclusion

Atypical microglandular adenosis (AMGA) was supposed to be a potential precursor of invasive carcinoma. Several studies have suggested the hypothesis that this uncommon, benign breast lesion could be involved in the mechanisms of multistep cancerization from normal breast tissue to a specific subset of triple negative and basal-like carcinomas, with distinct biological and immunohistochemical characteristics (positive for S-100, EGFr, p53 and luminal cytokeratins as CK8 and 18; negative for Bcl-2 and HMW/basal cytokeratins as CK5 and 6) [1–3,28,29]. Interestingly, MGA, AMGA and invasive carcinoma arising within AMGA have a common immunohistochemical profile, with the coexistence of basal-like (EGFr expression and Triple Negative phenotype) and luminal features (luminal cytokeratins as CK8 and 18) suggesting that they could originate from an “intermediate cell” with both glandular and basal differentiations [26,27]. BRCA1 syndrome is an autosomal dominant hereditary syndrome associated with a markedly increased susceptibility to breast and ovarian tumors, attributable to germline mutations in the BRCA-1 gene, with a cumulative risk of breast cancer by the age of 70 years of about 55–65% [4,5]. The BRCA-1 gene maps to 17q21 and encodes a nuclear protein of 1863 amino acids, with a RING finger domain at the N-terminus mediating the interaction with BARD1, which confers an E3-ubiquitin ligase activity on the complex [31]. The exact cellular function of the BRCA1 protein is still unclarified and actually it is unknown which proteins are targeted by the activity of the BRCA1/BARD1 complex. However, mutations in BRCA1 have been shown to sensitize cells to a variety of DNA-damaging agents, disrupting the G2/M cell-cycle checkpoint, also interacting with BRIP1 (Fanconi Anemia gene) [32].

Chromosomal and aCGH analyses display that breast carcinomas arising in BRCA1 mutation carriers, despite a distinct pattern of genetic aberrations, often harbour gains and losses affecting multiple chromosomal regions and point mutation, similar to those observed in carcinoma arising in a background of AMGA (gains of 8q and high frequency of p53 mutations) [3,29,33–35]. Nevertheless, at the present time, no significant correlation between BRCA-1 germline mutation, atypical microglandular adenosis (AMGA) and invasive carcinoma was documented [23,10] and, to our knowledge, only a case of MGA in a patient with BRCA-1 mutation has been described in literature, focusing on radiological features but lacking histological findings [10]. It is possible that the peculiar correlation between AMGA, invasive carcinoma and germline BRCA1 mutation has often been underestimated because of the rapid growth of the high-grade triple negative that masks the “precursor lesion” [1,20]. The relative rarity of AMGA as a pure lesion suggests a rapid transition to invasive carcinoma once specific genetic mutations, yet under investigation, develop [23,29,30].

Our case supports the hypothesis that microglandular adenosis (MGA) and atypical microglandular adenosis (AMGA) could be involved in the development of a specific subset of triple negative and basal-like breast carcinomas, also in patients with BRCA-1 germline mutation. In our case in fact, the invasive carcinoma showed, as already suggested by Khalifeh et al. [26] and Badve et al. [27], a coexistence of basal-like and luminal features, reflecting a probable origin from an intermediate cell with both glandular and basal differentiation. In addition, in agreement with other studies [1,23,29,30], our report underlines that in the multistep cancerization process of these tumors “p53 mutations” play a crucial role, as shown by the high percentage of positivity for p53.
detected in the invasive component of our case (100%, see Table 1) and by the increasing percentage of positivity for p53 passing from MGA and AMGA to invasive carcinoma (Fig. 7). A revolutionary approach, performed by Guerini-Rocco et al. [28], shows that all cases of MGAs and/or AMGAs associated with triple negative breast cancer harbour identical p53 mutations and similar copy number alterations (affecting PTEN, PIK3CA, INPP4B, ERBB3 and FGFR2), quite differently from “pure MGAs” that lack clonal non-synonymous somatic mutations and display limited copy number alterations. These findings support the notion that a subset of MGAs and AMGAs, morphologically unpredictable, may constitute non-obligate precursors of a well defined subset of triple-negative and basal-like breast carcinomas, with a crucial but not exclusive role, played by p53 mutations. Geyer et al. [2], according to the results described by Shinet et al. [3], demonstrated that the majority of MGAs associated with invasive carcinomas harbour copy number aberrations, recurrent gains of 1q, 2q and 8q, losses of 14 (with discordant results regarding the amplification of MYC) and that the acquisition of additional genetic alterations is necessary in the progression from AMGA to an invasive component. These studies demonstrate the great genetic heterogeneity of MGAs and/or AMGAs and their potential role as precursors of a subset of triple-negative and basal-like carcinomas but, from a clinical endpoint, the problem of clarifying which MGAs progress to triple-negative invasive carcinomas and the real proportion of triple-negative invasive carcinomas that originate from MGAs remains unsolved. Further studies enrolling larger cohorts of pure MGAs, pure AMGAs, MGAs and/or AMGAs associated with invasive carcinomas are necessary to better investigate these aspects and to discover the molecular drivers involved in the progression from MGA and AMGA to an invasive carcinoma. Furthermore, we want to underline the complexity in distinguishing an AMGA from an invasive carcinoma, especially on core biopsy. Because of the presence of pseudoinfiltration, non-lobulocentric proliferation, lack of myoepithelial layer and the characteristic biomarker status, MGA and AMGA can be easily confused with an invasive carcinoma. This may be the reason of the wrong diagnosis on core needle biopsy in our case, where the atypical microglandular adenosis (AMGA) was erroneously diagnosed as an invasive carcinoma with acinic-like features with a Ki-67 value of 15% (where on the definitive mastectomy specimen the AMGA resulted in a Ki-67 of 15% and the invasive component with a Ki-67 of 77%, respectively). As previously mentioned, measuring p53 and Ki67 expression, in addition to a careful morphological examination, can be a reliable method to distinguish between AMGA and invasive carcinoma [26].

In conclusion, this is the first histological case report of a triple negative carcinoma arising within MGA and AMGA, in a patient with a germline BRCA-1 mutation. Despite the known relationship between germline BRCA-1 mutation and triple negative carcinoma, the genetic

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**Fig. 5.** Ki-67 showed a trend in increasing positivity from atypical microglandular adenosis (Fig. 5) to invasive carcinoma (Fig. 6), respectively 15% and 77% (original magnification ×40).

**Fig. 6.** P53 showed a trend in increasing positivity from atypical microglandular adenosis (black arrow) to ductal carcinoma in situ arising within microglandular adenosis (white arrow) to invasive carcinoma (red arrow) (original magnification ×30). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Fig. 7.** P53 showed a trend in increasing positivity from atypical microglandular adenosis (black arrow) to ductal carcinoma in situ arising within microglandular adenosis (white arrow) and to invasive carcinoma (red arrow) (original magnification ×30). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Fig. 8.** Atypical microglandular adenosis lacks myoepithelial cells, as highlighted by antibodies raised against smooth muscle myosin-SMM. Note the internal control, represented by normal breast ducts (original magnification ×60).
and pathologic correlations connecting MGA, AMGA, invasive carcinoma and germline BRCA-1 mutations have not yet been investigated and this study reinforces and supports the hypothesis of a possible link between these entities. Future studies are needed to better investigate the molecular and pathologic aspects behind this interesting and fascinating field of human pathology, a promising area to obtaining an appropriate therapeutic approach.

References


[13] J. Hicks, A. Krasnitz, B. Lakshmi, et al., Novel patterns of genome rearrangement and pathologic correlations connecting MGA, AMGA, invasive carcinoma and germline BRCA-1 mutations have not yet been investigated and this study reinforces and supports the hypothesis of a possible link between these entities. Future studies are needed to better investigate the molecular and pathologic aspects behind this interesting and fascinating field of human pathology, a promising area to obtaining an appropriate therapeutic approach.