Original Article

Carcinoma arising in microglandular adenosis of the breast: triple negative phenotype with variable morphology

Fangfang Zhong¹,², Rui Bi¹,², Baohua Yu¹,², Yufan Cheng¹,², Xiaoli Xu¹,², Ruohong Shui¹,², Wentao Yang¹,²

¹Department of Pathology, Cancer Center, Fudan University, Shanghai, China; ²Department of Oncology, Fudan University, Shanghai, China

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Abstract: Carcinoma arising in microglandular adenosis (MGACA) is an extremely rare subtype of breast carcinoma. In this study, clinicopathological analysis of MGACA from 11 Chinese patients was conducted. Microscopically, all cases showed a spectrum of structure and glandular proliferations ranging from microglandular adenosis (MGA) to atypical MGA (AMGA) to MGACA. Carcinoma components were composed of high grade ductal carcinoma in situ (DCIS) in 1 case and invasive carcinoma in 10 cases. Invasive carcinomas were grade 3 in 10 tumors and grade 2 in 1. Invasive components in 5 of 10 cases were composed of invasive carcinoma of no special type (NST), and 1 case showed partially acinic cell differentiation. In 5 cases, invasive components were mixed of NST and matrix-producing carcinoma (MPC). All epitheliums in 11 cases were triple negative (ER-, PR-, HER2-), and diffuse positive for CK and S-100 protein. No myoepithelial cells were demonstrable from MGA to invasive components with immunohistochemical staining for P63 and calponin. PAS or reticulin stain showed the presence of a basement membrane around glands in MGA, AMGA, DCIS, and its absence in invasive components. Follow-up time ranged from 10 to 64 months. One patient developed a lung metastasis 24 months after surgery, 10 patients have been alive without recurrence. Our study revealed that MGACA is a distinct subset of breast carcinoma, with triple negative phenotype, high grade nuclear and variable morphology. Despite histopathologic and immunohistochemical features usually associated with a poor prognosis, MGACA seems to have a relatively favorable outcome.

Keywords: Breast carcinoma, microglandular adenosis, matrix-producing carcinoma, triple-negative phenotype, morphology

Introduction

Microglandular adenosis (MGA) of the breast is an extremely rare benign lesion. The glands of MGA lack a surrounding myoepithelial cell layer so the lesion may mimic an invasive carcinoma [1]. Carcinoma arising in MGA (MGACA) has been reported in up to 27% of patients with MGA [2-7]. Given the fact that MGACA is rare, limited literature is available, and most common subtype of invasive components is invasive carcinoma of no special type [2-7]. In this study, we reported 11 cases of MGACA in Chinese patients, to better evaluate the clinicopathological features and immunophenotype of this rare subtype of breast carcinoma.

Materials and methods

Case selection

A search for carcinoma arising in microglandular adenosis (MGACA) was performed in the surgical pathology and consultation files of the Department of Pathology, Fudan University Shanghai Cancer Center, between 2008 and 2013. In totally 27982 cases of breast carcinoma, 11 cases were accepted as MGACA after a detailed clinicopathological and immunophenotypic analysis. All cases were confirmed by at least two senior pathologists. Available data including clinical presentations, therapeutic regimens and follow-up information were evaluated.
Table 1. Clinical features of 11 patients with MGACA of the breast

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Tumor size (cm)</th>
<th>LN status</th>
<th>Distant metastasis</th>
<th>Type of surgery</th>
<th>Chemotherapy</th>
<th>Adjuvant radiation</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>1.5</td>
<td>negative</td>
<td>negative</td>
<td>BCS*</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>1.6</td>
<td>negative</td>
<td>negative</td>
<td>BCS</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>3.0</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>1.7</td>
<td>negative</td>
<td>negative</td>
<td>BCS</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>3.0</td>
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<td>Mastectomy</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>2.8</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>5.0</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>1.5</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>1.8</td>
<td>negative</td>
<td>BCS</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>2.5</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>46</td>
<td>3.0</td>
<td>negative</td>
<td>negative</td>
<td>Mastectomy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*BCS indicates breast-conserving surgery.

Morphology and immunohistochemistry

Resection specimens of 11 MGACA were routinely processed, embedded in paraffin and stained with hematoxylin and eosin (H&E). The carcinomatous components of all cases were classified according to 2012 World Health Organization (WHO) Classification of Tumours of the Breast [8], and graded according to the Elston-Ellis modification of Scarff-Bloom-Richardson grading system [9].

Immunohistochemical study was performed on paraffin-embedded sections from all cases by the standard Envision method using a panel of antibodies: estrogen receptor (ER) (1D5, dilution 1:150; DAKO), progesterone receptor (PR) (PgR636, dilution 1:125; DAKO), HER2 (polyclonal, dilution 1:175; DAKO), cytokeratin (CK) (M0821, dilution 1:200; DAKO), S-100 protein (polyclonal, dilution 1:300; DAKO), P63 (4A4, dilution 1:100; DAKO), calponin (CALD, dilution 1:150; DAKO), Ki-67 (MIB-1, dilution 1:100; DAKO). Appropriate positive and negative control samples were used. Periodic acid-Schiff (PAS) or reticulin stain was performed on all cases.

Evaluation of the staining

The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) immunohistochemical scoring criteria [10, 11] were used for determining ER, PR and HER2 status. For ER and PR, nuclear staining in ≥ 1% of the tumor cells was considered positive. HER2 immunoreactivity was evaluated on a standardized scale based on the intensity of membranous staining and the proportion of staining of invasive tumor cells, and continuous strong complete membranous staining in >10% of tumor cells was considered positive. Samples were defined as immunopositive if they had the following: nuclear staining for Ki-67; nuclear/cytoplasmic reactivity for S-100; membranous/cytoplasmic reactivity for CK, CK5/6 and calponin. Ki-67 labeling index was determined by counting the number of positive cells in a total of 1000 tumor cells.

Results

Clinical data

A summary of clinical features of each case is provided in Table 1. Eleven patients were female and ranged in age from 34 to 61 years, with a median age of 46. Five tumors were located in left breast and 6 lesions in right. All patients expressed a palpable mass. At the time of initial diagnosis, no patient had distant metastasis. Seven patients underwent mastectomy and 4 patients underwent breast-conserving surgery. One patient received neoadjuvant chemotherapy before the operation and all patients received adjuvant chemotherapy. Four patients who underwent breast-conserving surgery received postoperative radiation therapy. No axillary lymph nodes metastasis was found in 11 cases. Follow-up time ranged from 10 to 64 months. One patient developed a lung metastasis 24 months after surgery, 10 patients have been alive without recurrence.

Pathological features

The pathological features of 11 cases of MGACA are summarized in Table 2. The tumors
ranged from 1.5 to 5.0 cm in size, with a median diameter of 2.5 cm. All tumors were irregularly shaped with ill-defined periphery. Nearly all tumors were moderately firm to hard, with white to grey in cut surface. In 5 tumors, there was mucoid or glistening in some areas.

Microscopically, all cases showed a spectrum of structure and glandular proliferations ranging from MGA to atypical MGA (AMGA) to MGACA. The areas of MGA (Figure 1A) consisted of small round glandular structures infiltrating fibrous or fatty mammary stroma. The glands were lined by a single layer of cuboidal epithelial cells with round nuclei and abundant vacuolated cytoplasm. Eosinophilic material was seen in the open lumen. The areas of AMGA (Figure 1B) consisted of more irregularly shaped glands with less prominent intraluminal secretions and the epithelium exhibited coarse chromatin, and prominent nucleoli. The cytoplasm was dense, with a higher nuclear-to-cytoplasmic ratio. Scattered apoptotic and mitotic cells were present.

Carcinoma components were composed of ductal carcinoma in situ (DCIS) with high grade in 1 case. In the areas of DCIS (Figure 1C), the glands showed marked cytologic atypia, obliteration of the glandular lumen and frequent mitotic figures. But the underlying growth pattern of microglandular adenosis was still retained and no desmoplastic reaction was observed.

Ten cases showed a spectrum from MGA to AMGA to DCIS, and to invasive carcinoma. In the areas of invasive carcinoma, the tumor cells were arranged in cords, clusters, and solid nests. Desmoplastic stromal reaction and lymphocytic infiltration around invasive components were observed. Invasive components were mostly high grade with variable morphology. Invasive tumors were grade 3 in 10 cases and grade 2 in 1. In 5 cases, invasive components were composed of invasive carcinoma of no special type (NST) (Figure 1D). One of 5 cases showed partially acinic cell differentiation with prominent oncocytic change and eosinophilic cytoplasmic granules in a considerable portion of epitheliums in the areas of MGA (Figure 1E), AMGA, DCIS and NST (Figure 1F). In 5 cases, invasive components were mixed of NST and matrix-producing carcinoma (MPC) (Figure 1G, 1H). NST was observed in some areas of these cases, and an abrupt transition from invasive carcinoma to chondromyxoid matrix without an intervening spindle cell sarcomatoid component was showed in other areas. No osseous component was observed in 5 cases. In the case received neoadjuvant chemotherapy, minimal response was observed. The tumor cells were focally degenerated with stromal fibrosis and chronic inflammatory cells infiltration.

**Immunohistochemical and special stain findings**

All epitheliums (MGA, AMGA, MGACA) in 11 cases were triple negative (ER-, PR-, HER2-), and diffuse positive for CK and S-100 protein (Figure 2A). Ki-67 proliferation index ranged from 30% to 70% in 11 cases. No myoepithelial cells were demonstrable in MGA, AMGA, DCIS and invasive components with immunohistochemical staining for P63 and calponin (Figure 2B).
Breast carcinoma arising in microglandular adenosis

Figure 1. Carcinoma arising in microglandular adenosis (MGA). A. The areas of MGA consisted of small round glandular structures infiltrating fibrous and fatty mammary stroma, composed of small round glands lined by single layer of epithelial cells with vaculated cytoplasm and luminal eosinophilic secretions (H&E, ×100); B. Atypical MGA (right) are composed of atypical complex glands displaying nuclear pleomorphism, compared to the areas of MGA (left) (H&E, ×200); C. Ductal carcinoma in situ. The glandular lumen is obliterated by the proliferation of marked atypical cells (H&E, ×400); D. Tumors cells of invasive ductal carcinoma are arranged in irregular tubules and cords in the stroma (H&E, ×200); E. F. Carcinoma arising in MGA with acinic cell differentiation: E. Epitheliums in the areas of MGA show prominent eosinophilic cytoplasm (H&E, ×200); F. Infiltrating tumor cells arranged in single and clusters in the stroma exhibit extensive oncocytic change (H&E, ×200); G, H. Matrix-producing carcinoma arising in MGA: G. A transition from atypical MGA (left) to matrix-producing carcinoma (right) (H&E, ×100); H. A transition from invasive carcinoma to chondromyxoid matrix without an intervening spindle cell sarcomatoid component (H&E, ×400).

Discussion

Microglandular adenosis (MGA) is a proliferative glandular lesion that mimics carcinoma clinically and pathologically. It was not well characterized as a clinicopathological entity until the publication in 1983 of three series totaling 29 patients [3, 12, 13]. This entity differs substantially in its structural features from lesions conventionally termed “adenosis”. The basic pattern of MGA is an infiltrative proliferative proliferation of small round glands in a fibrous or fatty mammary stroma. The round glands are lined by a single layer of flat to cuboidal epithelial cells with no surrounding myoepithelial cell layer. The epithelial cells of MGA are usually positive for cytokeratin, S-100 protein, but negative for ER, PR and HER2 [6, 14, 15]. No myoepithelial cells can be demonstrated around the glands in MGA, but staining for PAS, reticulin, type IV collagen or laminin can confirm the presence of a basement membrane in MGA. MGA is most often mistaken for tubular carcinoma [12]. In contrast to the round glands of MGA, those of tubular carcinoma are typically angulated, and intraductal carcinoma is present in some tubular carcinomas. The cells of tubular carcinoma are positive for ER and PR, and the glands lack a basement membrane.

It is unclear whether MGA represents a truly benign proliferation or an indolent precursor lesion. Although ordinary MGA has been considered a benign proliferative lesion, atypical forms of MGA (AMGA) and invasive carcinomas arising in the background of MGA are recorded. Carcinoma has been found in up to 27% of patients with MGA. The role of microglandular adenosis as a potential precursor of invasive breast cancer has long been a matter of controversy. Molecular analysis [16-19] has demonstrated that at least a subset of MGA shows recurrent losses of chromosome 5q and gains of 8q. The pattern of genetic aberrations found in MGA differs from that of other non-obligate precursors of ER-positive breast cancer, and is reminiscent of those reported specifically for high-grade triple-negative breast carcinomas. These genomic alterations are shared with coexistent AMGA and DCIS and invasive carcinoma, supporting a precursor-product relation-
Breast carcinoma arising in microglandular adenosis (MGA) may be a non-obligate precursor of a subgroup of high-grade triple-negative breast carcinomas.

Several studies documented the progression of MGA to carcinoma in up to 27% of cases [2-7]. MGACA may show both in situ and invasive components. In our series, MGA progressed to DCIS in 1 case and invasive carcinoma in 10 cases. MGACA have a distinctive histopathological pattern. DCIS arising in MGA tends to retain the underlying alveolar growth pattern of MGA, and invasive carcinoma may exhibit associated desmoplastic reaction and infiltrating cords and individual cells. If extensive sampling has been performed, these cases may show a morphologic spectrum from MGA to AMGA to DCIS, and to invasive carcinoma. MGACA shared the same immunohistochemical profile of MGA [6, 14, 15], such as triple negative and positive for S-100. No myoepithelial cells can be demonstrated in MGA and related lesions. Staining for the basement membrane can confirm its presence in MGA, AMGA, DCIS and its absence in invasive carcinoma. In our series, all cases showed a clear transition from MGA to MGACA, and all epitheliums showed S-100 diffuse positive. Majority of cases (10/11) were high grade with high Ki67 index, all cases were triple negative, supporting the viewpoint that MGA may be a non-obligate precursor of a subgroup of high-grade triple-negative breast carcinomas.

The carcinomatous epitheliums of MGACA may exhibit cytoplasmic features found in MGA. The cytoplasm of epitheliums in majority of MGA may be clear or amphophilic, but pronounced eosinophilic cytoplasm may be encountered in a minority of cases. In 1 case of our series, acinar cell differentiation with prominent oncocytic change and eosinophilic cytoplasmic

Figure 2. Immunohistochemical features of carcinoma arising in microglandular adenosis (MGA). (A) Tumor cells are positive for S-100 (Envision, ×200); (B) Calponin staining confirms the absence of myoepithelial layer in MGA and related lesions (Envision, ×200); PAS staining shows the presence of a basement membrane around glands in MGA (Envision, ×200) (C) and its absence in invasive components (Envision, ×400) (D).
Breast carcinoma arising in microglandular adenosis

granularity were observed in a considerable portion of epitheliums of MGA, AMGA, DCIS and invasive carcinoma. MGACA with extensive oncologic change has been seldom detailed described in literature. In Rosen’s Breast Pathology [1], MGACA with eosinophilic cytoplasm is interpreted as invasive carcinoma with acinic cell differentiation arising in MGA. Acinic cell carcinoma of the breast carcinoma is a rare tumor similar to the acinic cell carcinoma of the parotid gland [20]. Two studies [21, 22] reported 2 case of acinic cell carcinoma arising in MGA, and suggested a close relationship between the two lesions. Nevertheless, some of the morphological, immunohistochemical and ultrastructural features of these lesions are different, so a histogenetic link remains to be proven.

NST is the most common type of carcinoma arising in MGA. Rare cases of adenoid cystic carcinoma, carcinoma with secretory differentiation, squamous metaplasia, chondromyxoid metaplasia, or basaloid features have been described occurring in association with MGA [5, 6, 23, 24]. In our series, NST could be observed in 10 cases of MGACA. In 5 cases, tumors were entirely composed of NST, in other 5 cases, tumors were mixed of NST and matrix-producing carcinoma (MPC). MPC is a rare subtype of metaplastic carcinoma, first described by Wargotz and Norris in 1989 [25]. The major criterion for a diagnosis of MPC is the presence of overt carcinoma with direct transition to a cartilaginous and/or osseous stromal matrix without an intervening spindle cell zone or osteoclastic cells. Benign chondromyxoid metaplasia of the stroma has been described in a minority of MGA [2]. MPC arising in MGA is an extremely rare subtype of breast carcinoma, and has been seldom detailed described in the previous studies [6, 23]. In our series, a considerable high portion (50%) of MGACA composed partially of MPC. This proportion may be slightly biased according to limited number of cases. However, MPC has similar immunohistochemical profile of MGA, such as triple negative and positive for S-100. Whether there is some relationships between these two lesions need to be further studied.

It is unclear whether MGA represents a truly benign proliferation or an indolent precursor lesion, so current recommendatory management of MGA is complete excision [1]. The excision specimens need to be sampled thoroughly to rule out the possibility of an associated carcinoma. Patients with AMGA should undergo wide excision with clear margin and careful follow-up [1]. Patients with MGACA should undergo mastectomy or breast-conserving surgery, and with adjuvant chemotherapy or radiation therapy if necessary. Prognosis of MGACA is controversial in literature [1, 4, 6]. In our study, only 1 patient developed a lung metastasis 24 months after surgery, 10 patients have been alive without recurrence after 10 to 64 months of follow-up. Despite histopathological (high nuclear grade) and immunohistochemical features (triple negative, high Ki-67 index) usually associated with a poor prognosis, it shows that majority of patients with MGACA in our series have a relatively favorable outcome.

In conclusion, our study revealed that MGACA is a distinct subset of breast carcinoma, with triple negative phenotype, high grade nuclear and variable morphology. Despite histopathologic and immunohistochemical features usually associated with a poor prognosis, majority of patients with MGACA have a relatively favorable outcome in our series. Recognition of this unusual subtype of breast carcinoma in routine work may have obvious clinical significance. Since MGACA is so rare, the prognosis of this tumor needs to be further studied with more cases and longer follow-up.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ruohong Shui, Department of Pathology, Cancer Center, Fudan University, 270 Dongan Road, Shanghai, China; Department of Oncology, Fudan University, 270 Dongan Road, Shanghai, China. Tel: 86-21-64175590-88313; Fax: 86-21-64046008; E-mail: shuirh@hotmail.com

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