Histol Histopathol (2013) 28: 1099-1108
DOI: 10.14670/HH-28.1099

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

Microglandular adenosis: a non-obligate precursor of triple-negative breast cancer?

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Summary. Microglandular adenosis is a rare glandular lesion of the breast, which can mimic well-differentiated invasive carcinoma, and is characterized by a haphazard proliferation of uniform small round glands with open lumina and lacking a myoepithelial cell layer. This lesion has a rather unique immunohistochemical profile characterized by expression of cytokeratins and S-100, and lack of estrogen receptor (ER) and progesterone receptor (PR). The role of microglandular adenosis as a potential precursor of invasive breast cancer has long been a matter of controversy; however, recent molecular analyses have demonstrated that these lesions are heterogeneous at the genetic level, and that at least a subset of microglandular adenosis are clonal and display gene copy number alterations. Importantly, the pattern of genetic aberrations found in microglandular adenosis differs from that of other non-obligate precursors of ER-positive breast cancer. Carcinomas arising in microglandular adenosis are mostly of triple-negative phenotype (i.e. lack of ER, PR and HER2) and express S100, similar to microglandular adenosis. Genetic alterations found in microglandular adenosis have been shown to be similar to those found in synchronous invasive carcinomas. Here we review the clinical, morphological, and molecular features of microglandular adenosis, with an emphasis on its role as a non-obligate precursor of triple-negative breast cancer, and discuss areas for future research endeavors to clarify the clinical and biological significance of these fascinating lesions.

Key words: Microglandular adenosis, Atypical microglandular adenosis, Triple-negative, Precursor, Breast cancer

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Introduction

Breast cancer is a complex disease, encompassing multiple entities that have been shown to display not only distinct clinical and histological features, but also to harbor distinct molecular characteristics and to be underpinned by distinct repertoires of genetic aberrations (Reis-Filho and Pusztai, 2011; Cancer Genome Atlas, 2012; Stephens et al., 2012; Weigelt et al., 2012). In fact, estrogen receptor (ER)-positive and ER-negative breast cancers have been shown to constitute fundamentally different diseases that arguably only share in common the facts that they affect the same anatomical site (i.e. breast) and originate in the same microanatomical structure (i.e. the terminal duct-lobular unit (TDLU)) (Reis-Filho and Pusztai, 2011; Weigelt et al., 2012).

The analyses of potential precursors of breast cancer, albeit not as complete as the study of invasive lesions, have yielded fascinating insights into their biology and clinical behavior (reviewed in (Lopez-Garcia et al., 2010)). It is currently accepted that some of the lesions once thought to be precursors of breast cancer (e.g. hyperplasia of usual type) are likely not related to breast cancer development, whereas other lesions (e.g. flat epithelial atypia (FEA)) have emerged as precursors of ER-positive ductal carcinomas *in situ* (DCIS) and lobular neoplasia (Lopez-Garcia et al., 2010). The basis for these conclusions lies on observational studies (Abdel-Fatah et al., 2007, 2008) and molecular analyses (Boecker et al., 2002; Simpson et al., 2005), which have shown that FEA, ER-positive DCIS and lobular neoplasia co-exist at a frequency greater than expected by chance (Abdel-Fatah et al., 2007, 2008), and, most importantly, that these lesions share specific genetic aberrations (e.g. deletions of 16q, gains of 1q and 16p) (Boecker et al., 2001; Simpson et al., 2005; Dabbs et al., 2006; Lopez-Garcia et al., 2010; Hernandez et al., 2012; Troxell et al., 2012). A question that remains

unanswered, however, is what the precursors of ER-negative DCIS and ER-negative breast cancers are.

Microglandular adenosis (MGA) is a rare epithelial lesion of the breast first described by McDivitt et al. (1968). Fourteen years later, in 1983, the clinical and pathological features of MGA were further illustrated in three studies (Clement and Azzopardi, 1983; Rosen, 1983; Tavassoli and Norris, 1983). Despite the initial debate on whether these lesions would be neoplastic rather than hyperplastic (Tavassoli and Norris, 1983) and whether they would constitute potential precursors of specific subtypes of breast cancer, independent groups have recently provided observational (Rosenblum et al., 1986; James et al., 1993; Koenig et al., 2000; Acs et al., 2003; Resetkova et al., 2003; Khalifeh et al., 2008; Shin et al., 2009) and molecular (Geyer et al., 2009, 2012; Shin et al., 2009) data to suggest that at least a subset of these lesions may constitute non-obligate precursors of a variety of invasive breast cancers that lack ER, progesterone receptor (PR) and HER2 expression (i.e. triple-negative breast cancers).

In this review, we discuss the morphological and immunohistochemical features of MGA, the molecular characteristics of this process, and its potential role as a non-obligate precursor of triple-negative breast cancer.

Clinicopathological characteristics

MGA can be either an incidental microscopic finding or can form a clinically palpable mass. These lesions affect women, whose age is reported to range from the 3rd to 9th decades (mean and median ages of 50-60 years) (Clement and Azzopardi, 1983; Rosen, 1983; Tavassoli and Norris, 1983; Khalifeh et al., 2008; Geyer et al., 2009, 2012; Shin et al., 2009). MGA can be unifocal or multifocal, and the size of the lesion ranges from 0.3 cm up to 20 cm in various studies (Clement and Azzopardi, 1983; Rosen, 1983; Tavassoli and Norris, 1983; Khalifeh et al., 2008). Mammographic findings are non-specific and may show mass formation or distortion. In a case report of MGA found at surveillance screening in a 22 year-old *BRCA1* germline mutation carrier, mammogram revealed dense breast with no abnormality. Sonography demonstrated a hypoechoic mass with irregular border, and magnetic resonance imaging (MRI) showed a small non-circumscribed mass with moderate early and delayed enhancement (Sabate et al., 2002).

MGA is characterized by a proliferation of small round glands lined by a single layer of cuboidal epithelial cells with clear/vacuolated or eosinophilic cytoplasm and uniform nuclei (McDivitt, 1968; Clement and Azzopardi, 1983; Rosen, 1983; Tavassoli and Norris, 1983). Unlike other intraductal proliferations and other forms of adenosis, the cells that line the glands that constitute MGA do not have cytoplasmic protrusions or apical snouts, and myoepithelial cells are entirely absent. The glands usually have open lumina containing inspissated secretion forming eosinophilic globules. The secretions are Periodic acid-Schiff (PAS)-positive diastase-resistant, and can be also positive for mucicarmine and alcian blue. The glands in MGA are generally haphazardly arranged, growing in adipose tissue or stroma without associated tissue reaction (Fig. 1). Despite the lack of myoepithelial cells, a discrete layer of periglandular reticulin has been consistently documented (Clement and Azzopardi, 1983), and, ultrastructural studies have demonstrated that the glands of MGA are surrounded by a multilayered basement membrane (Tavassoli and Norris, 1983).

The absence of myoepithelial cells encasing the glands of MGA has baffled pathologists since its original description. In fact, despite the absence of a myoepithelial layer, in a way akin to *bona fide* invasive breast lesions, the true nature of MGA has long been a matter of controversy. While some believed that it would be a mere benign lesion (Tavassoli and Norris, 1983) despite the absence of myoepithelial cells, others hypothesized that it could constitute a precursor of invasive breast cancer (Rosenblum et al., 1986; Khalifeh et al., 2008; Geyer et al., 2009, 2012; Shin et al., 2009), or even a form of ER-negative invasive breast cancer with a remarkably indolent clinical behavior.

Atypical MGA (AMGA) refers to lesions having recognizable features of MGA but exhibiting glandular structures of greater architectural complexity and some degree of cytological atypia, while lacking features of frank carcinoma (Rosenblum et al., 1986), including stromal reaction. The glands in AMGA are composed of a mixture of small round and larger elongated and tubular structures, with luminal bridging, stratification, and solid nests in a back-to-back fashion. Mild to moderate cytological atypia and infrequent mitotic figures can be seen. Intraluminal secretion is generally diminished or absent in AMGA (Fig. 2). It should be noted that the degree of cytological complexity may be compatible to that of atypical ductal hyperplasia and low-grade DCIS, which may result in a misdiagnosis by the unwary.

The morphological features of MGA mimic tubular carcinoma (TC) and therefore can be mistaken for well-differentiated invasive carcinoma. The following features can help to distinguish MGA from TC: the glands of MGA are small, round and relatively uniform in size and shape, while the glands in TC are irregular in size, shape, and have angulated contours. The cells in MGA have clear or, less frequently, vacuolated cytoplasm. The cytoplasmic apical snout is absent in MGA, while it is prominent in TC. The stroma in MGA is usually hypocellular and hyalinized, while there is frequent stromal desmoplasia in TC. MGA and TC also have distinguishing immunophenotypic features, as discussed below. In brief, while MGA cells consistently lack the expression of ER, TC, atypical ductal hyperplasia and low-grade DCIS are ER-positive.

MGA could also be confused with adenosis or variants of adenosis, such as sclerosing adenosis, apocrine adenosis, secretory adenosis, and tubular

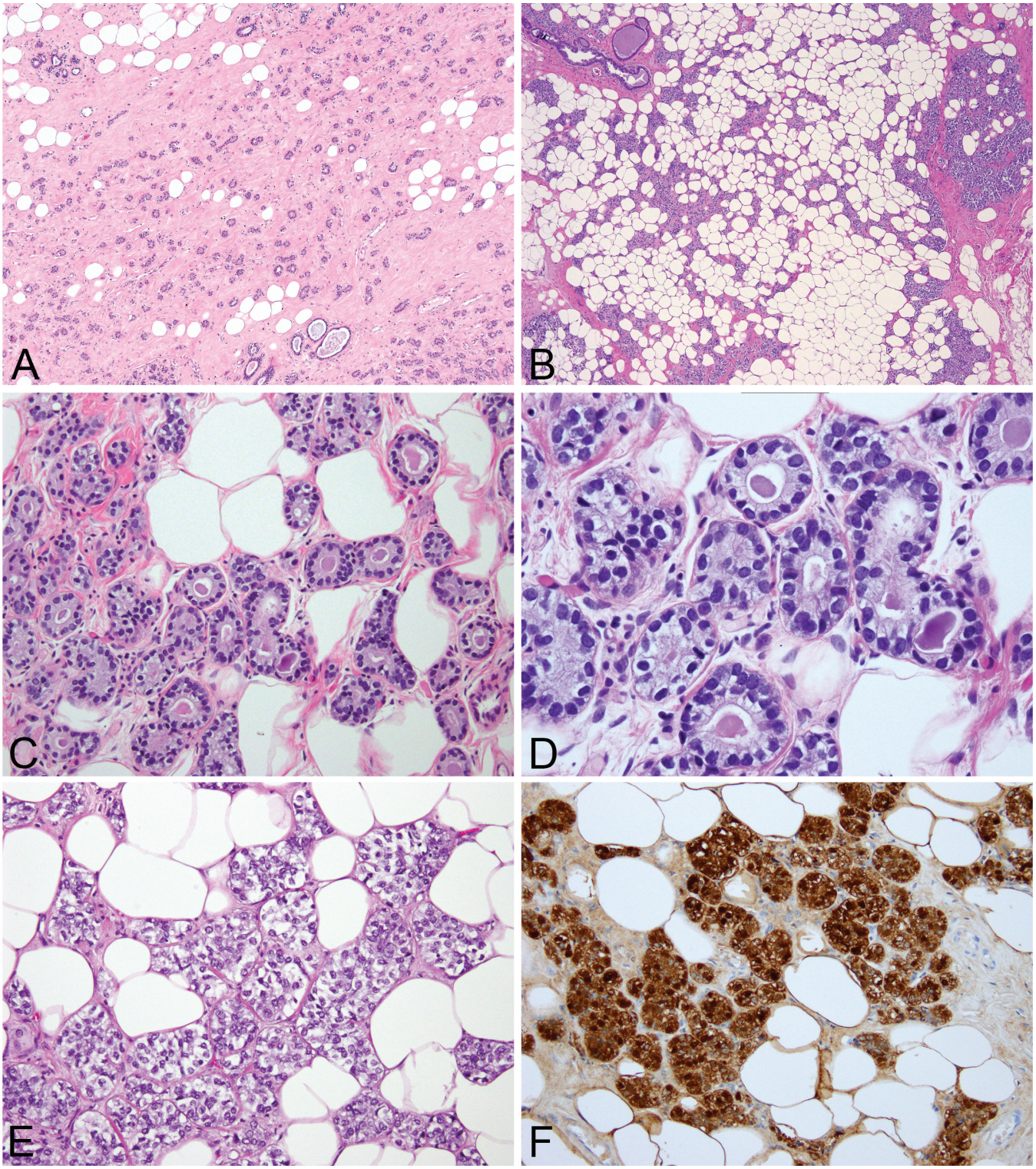

Fig. 1. Microglandular adenosis. Microglandular adenosis is characterized by a proliferation of haphazardly arranged glands, infiltrating the breast tissue without eliciting a stromal reaction **(A)**. These glands often infiltrate adipose tissue **(B)**. The epithelial cells of microglandular adenosis are cuboidal-to-columnar, with relatively monomorphic nuclei, and eosinophilic or clear cytoplasm **(C and D)**. The glandular structures are well formed, with open lumina often containing inspissated secretion forming eosinophilic globules **(C and D)**. Note that the lack of architectural and cytological atypia, and the absence of a myoepithelial layer surrounding the epithelial cells **(D)**. Microglandular adenosis can also be composed of cells with ample, clear cytoplasm **(E)**, and consistently express S-100 protein **(F)**.

adenosis. In a retrospective study, out of 65 cases initially diagnosed with MGA, 54 (83%) were later excluded based on the presence of myoepithelial cells (Khalifeh et al., 2008). Among the 54 cases that were re-classified, 48 were adenosis (Khalifeh et al., 2008). Adenosis usually has a lobular configuration, and does not infiltrate adipose tissue. Sclerosing adenosis may simulate infiltrative growth, however, the glands in sclerosing adenosis are more compressed and lack secretions within the lumen. Importantly, the identification of a discrete layer of myoepithelial cells surrounding the gland formations rules out a diagnosis of MGA.

Complete excision of MGA is recommended, and patients should be advised to have close clinical follow-up. MGA may develop local recurrence if incompletely excised (Rosen, 1983; Tavassoli and Bratthauer, 1993). AMGA should be widely excised to achieve clear margins and patients followed as would women with other atypical forms of hyperplasia. Recurrence of AMGA as invasive carcinoma in a background of AMGA eight years following incomplete excision of the lesion has been reported (Khalifeh et al., 2008).

Immunohistochemical findings

Immunohistochemical studies of MGA and AMGA have demonstrated that these lesions have an immunohistochemical profile that renders them distinct from other forms of adenosis and low-grade *in situ* and invasive breast cancers. These studies not only have confirmed that, in contrast with other forms of adenosis,

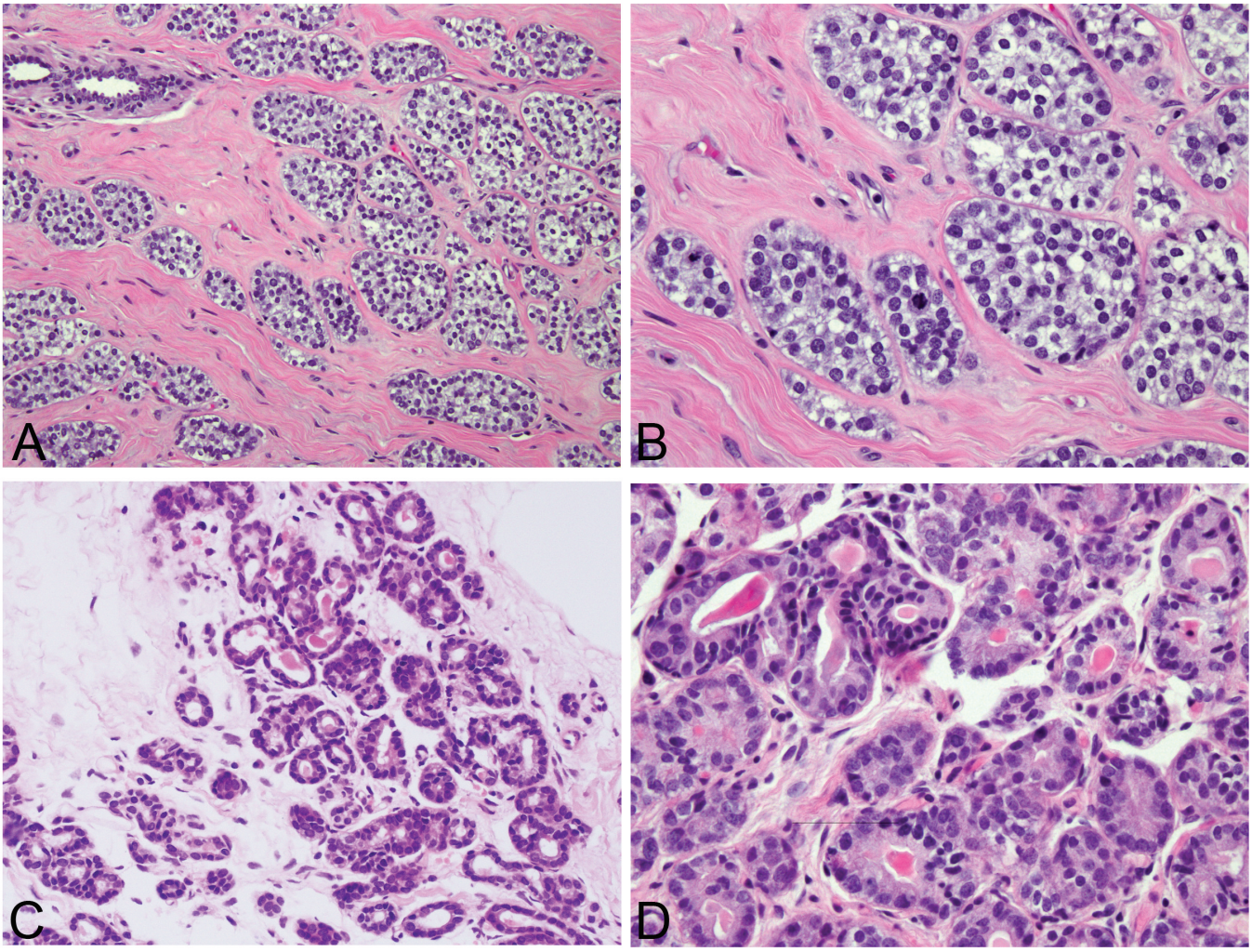

Fig. 2. Atypical microglandular adenosis. At variance with microglandular adenosis, atypical microglandular adenosis is characterized by the presence of architectural and cytological atypia. The gland formations become irregular, often lacking well defined lumina **(A, B and C)**. Trabeculae and nests of cells similar to those found in *bona fide* cases of microglandular adenosis can also be found in atypical lesions **(A)**. Greater nuclear pleomorphism and higher nuclear-cytoplasmic ratio are features of atypical microglandular adenosis cells **(B and D)**. Mitotic figures are not uncommonly found **(B)**.

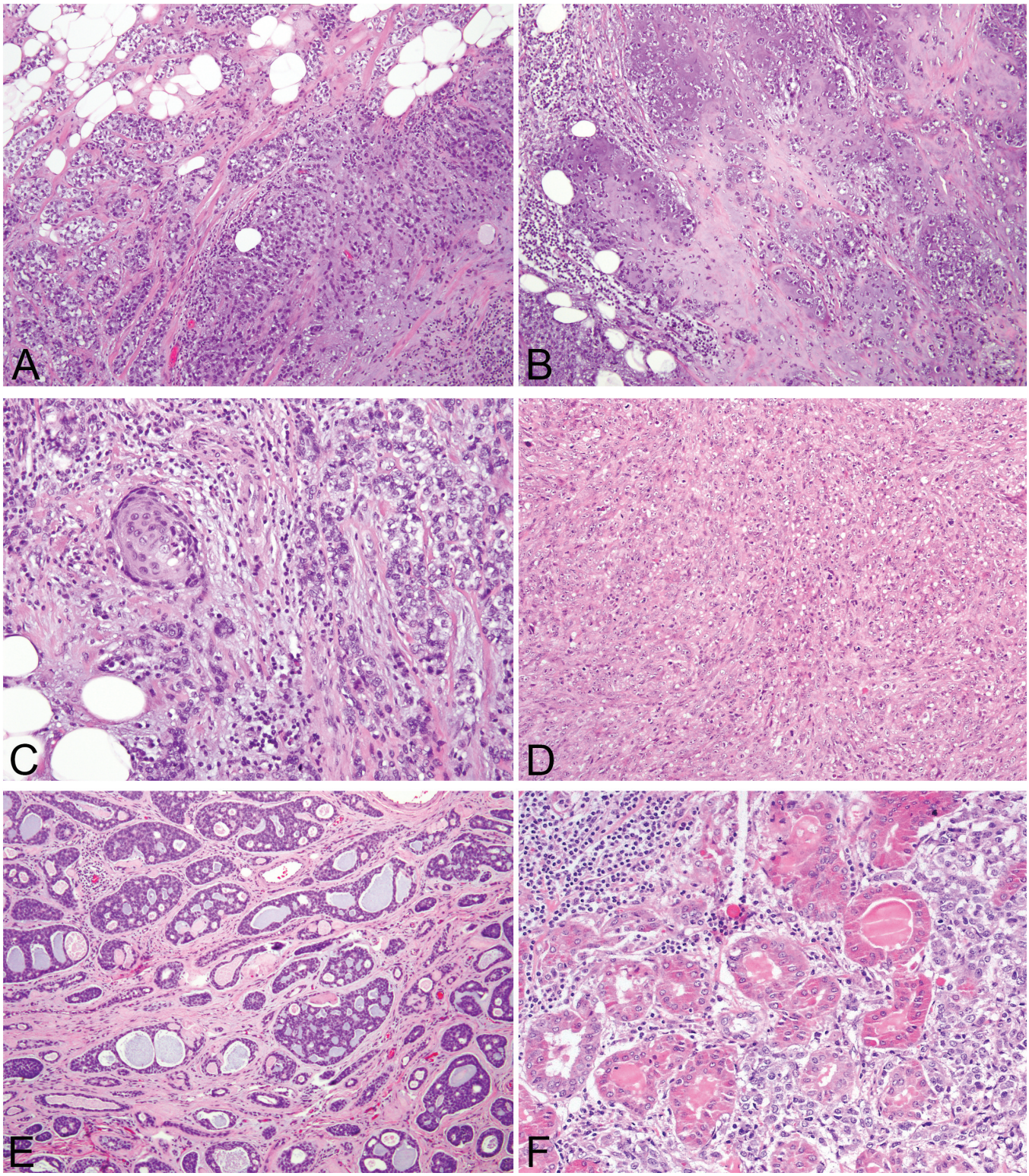

Fig. 3. Examples of triple-negative breast cancers developing in the context of microglandular adenosis and atypical microglandular adenosis. The vast majority of invasive breast cancers developing in the context of typical and atypical microglandular adenosis are of triple-negative phenotype (Table 2), and may present as high grade invasive carcinoma of no special type **(A)**, matrix producing breast carcinomas **(B),** metaplastic carcinomas with squamous elements **(C)** or sarcomatoid components **(D)**. Rare types of low-grade triple-negative breast cancers have also been reported in the context of typical and atypical microglandular adenosis, including adenoid cystic carcinoma **(E)** and acinic cell carcinoma **(F)**. Note in A the presence of a residual area of atypical microglandular adenosis (left) merging with the high grade invasive carcinoma of no special type (right).

MGA/ AMGA are characterized by the absence of myoepithelial cells and the presence of surrounding basal lamina highlighted by immunoreactivity for laminin and type IV collagen (Eusebi et al., 1993; Tavassoli and Bratthauer, 1993), but also that MGA and AMGA cells have a discrete immuno-phenotype. The epithelial cells of MGA/ AMGA express pan-cytokeratin AE1:AE3, CAM5.2, luminal cytokeratins CK8/18, cathepsin, epidermal growth factor receptor (EGFR), and show variable expression of basal cytokeratins (CK5/6, CK14, CK17) (Eusebi et al., 1993; James et al., 1993; Tavassoli and Bratthauer, 1993; Khalifeh et al., 2008; Geyer et al., 2009, 2012). One of the striking features of MGA is that its neoplastic cells consistently express S100 protein. At variance with other low-grade breast cancer precursors and low-grade invasive breast cancers, MGA cells display a triple-negative phenotype (i.e. they lack ER, PR and HER2), and do not express gross cystic disease fluid protein (GCDFP-15). Epithelial membrane antigen (EMA), which is strongly expressed in low-grade invasive breast cancers, is either absent or only focally expressed in MGA (Table 1).

Molecular genetic features

High-resolution chromosomal comparative genomic hybridization (cCGH) and microarray comparative genomic hybridization (aCGH) analyses have identified DNA copy number alterations in a subset of MGA and AMGA cases, suggesting that these cases are clonal lesions (Geyer et al., 2009, 2012; Shin et al., 2009). It should be noted, however, that not all lesions displayed gene copy number aberrations, and that the evidence available to date suggests that MGA and AMGA constitutes a heterogeneous group of lesions at the genetic level.

In the lesions harboring copy number aberrations, copy number alterations were detected in an average of 12% of the genome in MGA, and an average of 21% of the genome in AMGA (Geyer et al., 2012). The most common gene copy number changes reported in MGA are gains of 1q, 2q, 7p, 7q and 8q, and losses of 1p, 8p, 14q, 16q and 17q. Additional recurrent changes, such as gains of 6p and losses of 10q have been observed in AMGA (Geyer et al., 2012). Most importantly, in cases where MGA/AMGA and concurrent invasive triple-negative breast cancer were analyzed, the genetic aberrations found in MGA/AMGA were also identified in the adjacent invasive breast cancer, providing strong circumstantial evidence to suggest that MGA/AMGA constitute non-obligate precursors of triple-negative breast cancers (see below).

Another observation made in these studies was that the pattern of genetic aberrations found in MGA and AMGA was different from that of other known ER-positive non-obligate breast cancer precursors, such as atypical ductal hyperplasia (ADH) and FEA. Out of all MGA and AMGA lesions studied, only one AMGA displayed gain of 1q and loss of 16q (Geyer et al., 2009, 2012; Shin et al., 2009), the hallmark genetic aberrations found in ER-positive non-obligate breast cancer precursors (Lopez-Garcia et al., 2010). These observations suggest that the development and progression of MGA/AMGA involves alterations in a constellation of genes different from those involved in the genesis of ER-positive non-obligate precursors of breast cancer.

MGA as a non-obligate precursor lesion of triple-negative breast cancer

The precancerous nature of MGA was first suggested by Rosenblum et al. (1986). In 1986, the authors illustrated a series of seven breast carcinomas in

Table 1. Summary of immunohistochemical characteristics of MGA, AMGA, adenosis, low-grade invasive carcinoma and triple-negative breast cancer.

	MGA/AMGA	Adenosis	Low-grade invasive carcinoma	Triple-negative breast cancer
Laminin	+	+	-	-
Collagen IV	+	+	-/+*	-
Myoepithelial markers	-	+	-	-
EMA	-/+↓	+	+	-/+
Pan-cytokeratin	+	+	+	+
CK8/18	+	+	+	+/↓
HMW-CKs (CK5/6, CK14, CK17)	+/-	-	-	+
EGFR	+	-	-	+/-
ER	-	+	+	-
PR	-	+	+	-
HER2	-	-	-	-
S100	+++	- (E)/+ (ME)	-	+/-
GCDFP-15	-	+/-	+/-	-/+

AMGA, atypical microglandular adenosis; E, epithelium; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; ER, estrogen receptor; GCDFP, gross cystic disease fluid protein; HMW-CK, high molecular weight cytokeratin; ME, myoepithelium; MGA, microglandular adenosis; PR, progesterone receptor ; -, negative; +, positive; +++, strongly positive; ↓: reduced; *: a layer of collagen IV can be occasionally detected around glands of invasive tubular carcinoma.

association with MGA/AMGA. A spectrum of increasing architectural complexity and cytologic atypia in these cases suggested transitions from MGA to carcinoma. In some cases, the cells of the invasive carcinomas adjacent to MGA exhibited secretory activity reminiscent of that of MGA cells. The existence of a spectrum of lesions with progressive architectural and cytological atypia from MGA to AMGA to carcinoma, and the presence of unusual histological features in the carcinoma simulating MGA were considered by the authors as compelling morphological evidence that MGA might serve as a precursor lesion for the development of breast carcinoma. Subsequently, several other studies described breast carcinomas arising in, or in conjunction with, MGA (James et al., 1993; Koenig et al., 2000; Acs et al., 2003; Resetkova et al., 2003; Khalifeh et al., 2008; Geyer et al., 2009, 2012; Shin et al., 2009; Shui and Yang, 2009; Lee et al., 2010; Shui et al., 2011). The incidence of carcinoma ranged from 23% to 64% of patients with MGA in these studies. It should be noted, however, that the rate of 64% in one study may be an overestimation of the potential of progression of MGA to invasive breast cancer due to referral bias (Khalifeh et al., 2008).

The invasive breast carcinomas arising in this setting have exhibited a variety of histologic features, some harboring unusual clear cell components, displaying basal-like morphology, or manifesting metaplastic features with chondroid or sarcomatoid elements (Table 2, Fig. 3) (Rosenblum et al., 1986; James et al., 1993; Koenig et al., 2000; Acs et al., 2003; Khalifeh et al., 2008; Shui et al., 2011). Adenoid cystic carcinoma associated with MGA has also been reported (Acs et al., 2003; Khalifeh et al., 2008).

Immunohistochemical studies comparing MGA, AMGA and carcinomas arising in MGA have confirmed the transition. Invasive carcinoma arising in MGA shares a similar immunoprofile with MGA and AMGA, showing strong immunoreactivity for S100 protein (James et al., 1993; Koenig et al., 2000). There is gradually increasing expression of Ki67 and p53 from MGA to AMGA to carcinomas arising in MGA (James et al., 1993; Khalifeh et al., 2008). Invasive carcinomas arising in MGA are mostly triple-negative (i.e. ER-, PR-, and HER2-negative) (James et al., 1993; Koenig et al., 2000; Khalifeh et al., 2008). Basal markers, including EGFR and variable basal cytokeratins, and luminal cytokeratins CK8/18 are expressed in MGA, AMGA, and associated invasive carcinomas, suggesting a basal-like phenotype (Khalifeh et al., 2008; Geyer et al., 2009, 2012).

Recent molecular genetic studies further support the precancerous nature of MGA. Genomic analysis not only indicated that MGA is a clonal lesion, but also demonstrated that microdissected MGA, AMGA and invasive carcinoma arising in MGA from the same

Table 2. Summary of reported cases of invasive breast carcinoma arising in MGA/AMGA.

Year	Author	No. of patients	Age (y), range (mean)	Tumor size (cm), range (mean)	Histological features of invasive carcinoma	ER-	PR-	HER2-
1986	Rosenblum et al.	7	39-72 (54)	0.8-3.0 (2.5)	Clear cell (7/7) Granular cell (4/7) Matrix-producing (3/7)	ND	ND	ND
1993	James et al.	14*	26-68 (49)	1-5.5 (ND)	Matrix-producing (2/14)	7/8	6/8	7/8
2000	Koenig et al.	12	ND	ND	Clear cell (3/12) Basaloid (2/12) Matrix-producing (2/12)	7/8	8/8	ND
2003	Resetkova et al.	1	73	ND	IDC-NOS	1/1	1/1	1/1
2003	Acs et al.	17	40-86 (57)	0.6-11 (2.6)	Adenoid cystic (17/17)	ND	ND	ND
2008	Khalifeh et al.	6	30-65 (54)	1.2-3.0 (2.3)	Clear cell (6/6) Matrix-producing (4/6) Sarcomatoid (1/6) Acinic-like (2/6) Adenoid cystic (1/6)	6/6	6/6	6/6
2009	Shin et al.	8	28-86 (57)	ND	ND	ND	ND	ND
2009	Shui et al.	1	42	4.5	IDC-NOS	1/1	1/1	1/1
2009	Geyer et al.	1	74	ND	IDC-NOS	1/1	1/1	1/1
2010	Lee et al.	1	29	4.5	IDC-NOS	1/1	1/1	1/1
2011	Shui et al.	2	ND	ND	Matrix-producing (2/2)	2/2	2/2	2/2
2012	Geyer et al.	10**	ND	ND	Matrix-producing (1/2)	2/2**	2/2**	2/2**

*Including 7 patients previously reported by Rosenblum et al. (1986). **Including 2 new cases and 8 previously reported cases (Geyer et al. (2009); Khalifeh et al. (2008)). ER: estrogen receptor; IDC-NOS, invasive ductal carcinoma, not otherwise specified; ND, no data; PR: progesterone receptor; -, negative.

patient displayed similar genetic alterations (Geyer et al., 2009, 2012; Shin et al., 2009). In most cases, the invasive carcinoma arising in MGA is triple-negative and expresses basal markers, suggesting MGA is a non-obligate precursor of triple-negative and basal-like invasive breast carcinoma.

Triple-negative breast cancers are characterized by remarkable heterogeneity in terms of morphology, clinical behavior, and genomic alterations. In fact, the presence of MGA in association with triple-negative breast cancer has only rarely been reported. It is possible that MGA only exists as a transient stage. Since the genetic alterations have already occurred in MGA, the progression from MGA to invasive carcinoma might happen so rapidly that MGA is quickly taken over by invasive carcinoma without ever being detected. Because MGA is such a rare lesion, it is difficult to determine its biological behavior and the frequency with which it progresses to triple-negative breast cancer. Another potential explanation for the apparent rarity of MGA/AMGA in conjunction with a diagnosis of triple-negative breast cancer is that only a subset of triple-negative breast cancers is preceded by MGA/AMGA. If that is the case, studies addressing the question of whether the subset of triple-negative breast cancers associated with, or originating from, MGA/AMGA may have distinctive histopathological, molecular and/ or clinical characteristics are warranted.

The treatment of carcinomas arising in MGA follows the same general guidelines for breast carcinomas. Because of the rarity of the disease, follow-up studies are limited. It is not yet known whether carcinomas arising in MGA have unusual clinical behavior and outcome. One study reported relatively favorable prognosis for carcinomas arising in MGA, with a median follow-up of 57 months (James et al., 1993). Among 14 patients in this report, 10 patients were treated with radical mastectomy, 7 of whom also received adjuvant chemotherapy and/or radiation therapy. In another study, however, 2 (33%) out of 6 patients with carcinoma arising in MGA had distant metastasis at presentation and died of disease within 2 years (Khalifeh et al., 2008).

Conclusion

In summary, MGA is a clonal, neoplastic proliferation that mimics carcinoma clinically and pathologically. It is the only preinvasive mammary epithelial lesion in which a distinct myoepithelial layer is entirely absent. Early morphologic studies suggested that MGA would constitute a precancerous lesion. This notion has been recently corroborated by molecular studies, which have also revealed that a subset of MGA and AMGA are clonal and neoplastic, rather than hyperplastic. In addition, the presence of genetic aberrations similar to those found in synchronous adjacent triple-negative breast cancers provide strong circumstantial evidence to suggest that MGA and AMGA are non-obligate precursors of at least a subset of triple-negative breast cancers. Questions that are germane to our understanding of the clinical relevance of MGA and AMGA include how often these lesions progress to invasive breast cancer and the levels of risk of subsequent breast cancer development are conferred by a diagnosis of MGA and AMGA. Furthermore, how often MGA and AMGA are found in specimens obtained for the management of triple-negative breast cancers remains to be determined. Large, multi-institutional collaborations will certainly be required to address these questions.

Despite the evidence to demonstrate that MGA and AMGA are clonal and neoplastic, and that at least some of these lesions are likely to constitute non-obligate precursors of invasive breast cancer (Geyer et al., 2009, 2012; Shin et al., 2009), it is unclear as to whether the subsets of MGA/AMGA that lack genetic aberrations are dead-end lesions and not associated with a risk of breast cancer development. Finally, whether triple-negative breast cancers arising in the context of MGA/AMGA have distinct clinicopathological features and/ or are underpinned by a different repertoire of genetic aberrations remains to be fully elucidated. With the development of massively parallel sequencing and approaches to sequence minute lesions and individual cells (Aparicio and Huntsman, 2010; Natrajan and Reis-Filho, 2011; Navin et al., 2011), studies combining state-of-the-art pathology with cutting-edge molecular tools are essential to address these questions.

Acknowledgements. We thank Dr. Marc Rosenblum for his critical review of the manuscript.

Conflict of interests. The authors have no conflicts of interest to declare.

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Accepted March 18, 2013