Microglandular Adenosis

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Microglandular adenosis (MGA) is a rare breast lesion that is often detected incidentally and occasionally presents as a mass\(^1\). It has an infiltrative pattern and the glands are haphazardly distributed in a hypocellular or fibrous matrix with extension into fatty stroma (Fig. 1). The glands are small, round, uniform and lined by a single layer of flat to cuboidal epithelial cells. The cytoplasm may be vacuolated or granular. Absence of a myoepithelial layer is the sine qua non of this lesion (Fig. 2,3). In a retrospective review of 65 cases\(^2\) containing a diagnosis of MGA at MD Anderson, up to 85% were instead found to represent other forms of adenosis by virtue of an intact, SMA-positive myoepithelial layer. Nonetheless, its benign nature is affirmed by the presence of a surrounding multilayered basement membrane highlighted by stains for reticulin, type IV collagen (Fig. 4) and laminin\(^3\).

![Fig. 1.MGA: Glands infiltrating fat. H&E 20X](image1)

![Fig. 2 MGA: No staining for p63](image2)

![Fig. 3 MGA: No myoepithelial cells](image3)

![Fig. 4 MGA: Type IV collagen shows presence of basement membrane](image4)
The infiltrative pattern of growth may cause confusion with low-grade invasive ductal (tubular) carcinomas. The latter is distinguished by a stellate “tear-drop” growth pattern and a desmoplastic stromal response. In addition, the glands of MGA contain a characteristic PAS-positive, diastase-resistant, eosinophilic material not present in tubular carcinoma. The immunophenotypic profile is peculiar and further helps distinguish MGA from invasive carcinoma. The glands are S100 positive (Fig. 5, 10) and negative for estrogen/progesterone receptors (ER/PR) and HER-2 (Fig. 6) (triple-negative phenotype), but EGFR positive (Fig. 7, 8) (Table 1). In contrast to the strong EMA-positivity that is observed in benign and malignant glandular breast lesions, the epithelium in MGA is typically negative or only focally positive. Several studies suggest that MGA may represent a non-obligate precursor to invasive breast carcinoma based upon the presence of an invasive component in up to 27% of patients. A spectrum of microglandular proliferations from benign adenosis (Fig 1) to atypical MGA (Fig. 16) (AMGA) and breast carcinoma arising in MGA (MGACA) (Fig. 9) has been described. All three lesions may be present in a single case, (Figs.1-22) and are thought to represent true progression by virtue of a similar immunophenotypic profile and genetic constitution as illustrated by comparative genomic hybridization experiments. The glands of atypical MGA are more complex than those of MGA, with size and shape variation, epithelial stratification and readily apparent mitoses and apoptotic cells. Breast carcinomas that arise from such a background usually exhibit a solid growth pattern but may demonstrate features as diverse as metaplastic or adenoid-cystic phenotype. Regardless of their cytologic grade, however, invasive tumors arising from MGA are usually triple-negative for ER/PR/HER2 (Fig.6), similar to MGA and AMGA, and have a luminal phenotype (CK8/18 positive) (Fig. 13).

The progression of microglandular lesions from benign to frank carcinoma is characterized by accumulation of complex genetic abnormalities and by the morphologic features described above. In a study by Khalifeh et al, increasing nuclear reactivity for MIB-1 and p53 reflect this feature (Figs.17,19-22).
Fig. 7 MGA: EGFR positive (20X)

Fig. 8 Carcinoma arising in MGA: EGFR positive (20X)

Fig. 9 Carcinoma arising in MGA: H&E (20X)

Fig. 10 Carcinoma arising in MGA: S-100 positive (20X)

Fig. 11 Carcinomas arising in MGA: Cytokeratin 7 positive (20X)

Fig. 12 Carcinoma arising in MGA: GCDFP-15 negative (20X)
Fig. 13 Carcinoma arising in MGA Cytokeratin 8 positive (20X)

Fig. 14 Carcinoma arising in MGA: Cytokerative 5/6 negative (20X)

Fig. 15 MGA: CAM5.2 positive (20X)

Fig. 16 MGA with atypia H&E (20X)

Fig. 17 MGA: p53 negative (10X)

Fig. 18 MGA: Cytokeratin 5/6 negative (20X)
The following table demonstrates the utility of immunohistochemistry in distinguishing MGA from other lesions in the differential diagnosis.

### TABLE I:

**Utility of IHC in distinguishing MGA from other lesions**

<table>
<thead>
<tr>
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<th>MGA</th>
<th>AMGA</th>
<th>MGACA</th>
<th>Tubular Ca</th>
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<tbody>
<tr>
<td>S-100</td>
<td>++</td>
<td>++</td>
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<td>-</td>
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<td>EGFR</td>
<td>+</td>
<td>+</td>
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<tr>
<td>ER/PR</td>
<td>-</td>
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<td>++</td>
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<tr>
<td>HER2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>MIB-1</td>
<td>&lt;3%</td>
<td>5-10%</td>
<td>&gt;30%</td>
<td>&lt;10%</td>
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<tr>
<td>p53</td>
<td>&lt;3%</td>
<td>5-10%</td>
<td>&gt;30%</td>
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<td>EMA</td>
<td>+/-</td>
<td>+/-</td>
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Triple negative carcinomas have a poor prognosis and the pattern of metastasis is different than the usual type of infiltrating ductal carcinoma. Metastases to visceral organs like lung and brain is much more common than lymph node involvement. Carcinomas arising in microglandular adenosis are triple negative, but not of basal phenotype.
References