Atypical Microglandular Adenosis of the Breast, a Non-Obligate Precursor to Breast Invasive Carcinoma: Case Report and Review of the Literature

Benjamin Love¹, Christine Flores², Chelsea Adaeze Chibuzor³, Mikhail Johnson¹, Mary Rose Young⁴, Silas Morris², Jonathan Kwok², Fady Beshara², Jessica Jahoda¹,²*, Mohamed Aziz¹

Affiliations
¹Research Writing & Publication (RWP) LLC, NY, USA
²American University of the Caribbean Medical School, USA
³St George University School of Medicine, Grenada, West Indies
⁴Lake Erie College of Osteopathic Medicine (LECOM), PA, USA

Abstract:
Microglandular adenosis (MGA) is a benign breast tumor, but it is considered a non-obligate precursor to invasive breast carcinoma. MGA has a few different morphological variations, including microglandular adenosis (MGA), atypical microglandular adenosis (AMGA), and breast carcinoma-associated microglandular adenosis (BCMGA). Initially, with the identification of MGA, it was classified as a benign lesion; however, recent molecular studies have demonstrated an association between MGA, AMGA, and BCMGA. As a precancerous tumor, a definitive diagnosis of MGA is essential, including reporting the degree of atypia if present. We present the case of a 39-year-old woman whose routine mammogram revealed an irregular density, leading to her diagnosis of AMGA. We provide a brief review of the pertinent literature, including diagnosis, differential diagnosis, molecular studies, management, and outcome of MGA.

Keywords: Microglandular adenosis, Atypical, Benign, Malignant, Immunohistochemistry

Abbreviations: Microglandular adenosis (MGA), Atypical microglandular adenosis (AMGA), Breast carcinoma-associated microglandular adenosis (BCMGA), Immunohistochemistry (IHC), triple-negative breast carcinoma (TNBC)

Introduction:
Microglandular adenosis (MGA) is a rare, borderline neoplastic lesion found within the female breast and defined by the disordered proliferation of small, round glands within the stroma and adipose tissue.¹ Initially, the lesion was accurately described in 1983.² and was considered benign.³ However, extensive research reveals that MGA gives rise to invasive breast carcinoma (IBC) in 20-30% of cases.⁴ Moreover, MGA and its atypical variant, the atypical microglandular adenosis (AMGA), are non-obligate precursors to triple-negative breast cancers (TNBC). Histologically, the glands have flat to cuboidal epithelial cells completely invested by the basement membrane.⁵,⁶ The lesion is also characterized by its infiltration into the surrounding breast tissue, mimicking invasive carcinoma.⁷ While MGA is S-100 positive, it is also unique in that it is estrogen (ER) and progesterone receptor (PR) negative and does not show human epidermal growth factor receptor-2 (HER2) expression. In 27% of cases, MGA is expressed concurrently with invasive carcinoma.⁸ MGA has garnered unique classifications for its close association with invasive carcinoma, particularly in cases where they coexist within the same breast tissue. This interplay between benign and malignant lesions poses significant diagnostic challenges, necessitating meticulous histopathological examination for accurate differentiation.⁷ The absence of myoepithelial cells surrounding the glandular structures remains a hallmark feature of MGA, adding to the difficulty distinguishing it from invasive carcinoma, which also lacks the myoepithelial layer.¹

This rare condition often resembles benign and malignant lesions, particularly tubular carcinoma, and another invasive carcinoma.⁹ Accurate diagnosis is critical as it influences affected patients' clinical management and prognosis. MGA predominantly affects middle-aged women, though it can occur across a wider age range.⁸ Clinically, MGA can manifest as a palpable mass or be an incidental finding on imaging studies performed for unrelated reasons.¹⁰ Despite its benign nature, MGA's potential association with invasive carcinoma in some cases underscores the importance of thorough pathological evaluation and appropriate clinical follow-up.
Case Presentation:

A 39-year-old woman presented with an irregular dense nodularity of the right breast noted during routine mammography. Seven years ago, the patient had a hysterectomy and bilateral oophorectomy for dysfunctional uterine bleeding and fibroid uterus; otherwise, there was no significant medical history, including her family members. None of the patient's family had developed tumors before. On physical examination, there was no palpable breast mass or axillary lymphadenopathy. Routine laboratory tests were within the normal range, including routine blood examination and basic metabolic panel. The lesion showed iso- and slight hypo-density on ultrasound examination, and MRI showed a slightly hypoechoic region compared to surrounding fat. The lesional area showed higher T2 signal intensity.

To obtain a definitive diagnosis, the patient underwent a breast core biopsy. Microscopic examination of the biopsy showed randomly spaced, uniformly sized, spherical, open glands with eosinophilic secretions. The glands appeared to infiltrate the breast fatty tissue, but there was no dense stromal reaction to the infiltrating glands, which were lined-up with a single layer of cuboidal epithelial cells with clear, foamy, granulated, and some vacuolated cytoplasm containing eosinophilic secretions (Figure 1 A&B). Because the single epithelial layer lacked myoepithelium and the infiltrative stromal development, possible invasive carcinoma could not be ruled out. Immunohistochemistry (IHC) studies showed the glandular epithelium negative for ER, PR, and Her-2. In addition, myoepithelial markers were negative. S100 was found to be positive, which was not in support of breast ductal carcinoma. Because of the presence of a single layer of cells and the absence of myoepithelial cells by IHC studies, the mass was suspicious for IBC, and it was decided that the irregular nodular area with safe should be excised with safe surgical margins to evaluate the entire mass fully.

The area with the abnormality was excised with localization wire-guided lumpectomy. The specimen measured 4x3x1.8 cm and consisted of tissue indistinguishable from normal breast tissue but included scattered, dense white, tan areas, the largest 0.6 cm, without calcification. Microscopic examination of the excised tumor showed epithelial glandular atypia not seen in the prior core biopsy with increased active mitotic figures, glandular budding, luminal bridging, and loss of basement membranes confirmed with PAS stain (Figure C&D). The pathological differential included benign breast lesions in addition to low-grade variants of breast carcinoma. Benign lesions such as sclerosing adenosis were excluded by the absence of distorting fibrosis and the lack of the myoepithelial layer, which also did not favor apocrine adenosis. Well-differentiated invasive ductal carcinoma, tubular carcinoma, or even triple negative carcinoma (ER-, PR-, Her2-) were also not supported by strong positivity with S-100. The glandular epithelial cells were positive for cytokeratin AE2/AE3, S100, and cathepsin-D (Figure 2 A, B, C, D). With negative gross cystic disease fluid protein (GCDFP-15), negative myoepithelial markers actin, calponin, and SMMHC, the histomorphology and immunohistochemistry profile were consistent with diagnosing microglandular adenosis—the patient refused to perform further molecular testing on the excised lesion. Due to focal mild to moderate epithelial atypia and scattered few mitoses, the final diagnosis rendered was breast atypical micro glandular adenosis; all surgical margins were free of the lesion.

The lesional tissue was hormone receptors negative, and because chemotherapy is not typically used for post-operative excision of atypical micro glandular adenosis (AMGA), the patient was advised that surgical excision and close monitoring are the primary approaches. At the 28-month follow-up, there was no evidence of recurrence or abnormal changes in mammographic findings.

Discussion:

For the first time, MGA was depicted in print in 1968 and accurately described and histologically defined in 1983. That year, Tavassoli et al. reported that the entity is benign; nevertheless, now research has now come to a consensus that MGA is a non-obligate precursor to triple-negative breast carcinoma (TNBC). Despite the rarity of the entity (approximately 0.1% of breast biopsies), the entity is extremely rare, comprising approximately 0.1% of breast biopsies. Genetic instability that defines MGA lesions may give rise to invasive breast carcinomas (IBC) in 20-30% of the MGA cases. This makes this entity extremely sensitive to timely and accurate diagnosis because IBC, particularly TNBC, if not properly managed, are subject to poor prognosis. The lesion affects exclusively females within the 28 to 82 age range and mainly in the sixth decade of life, the lesions are present as palpable masses or may be identified incidentally. During physical examination, the masses vary between 3-4 cm and may be up to 20 cm.

A retrospective study conducted by Khalifeh et al. in 2008 looked at 108 cases with the diagnosis of MGA from 1983 to 2007 at the Andersen Cancer Center. Out of the 108 cases, only 65 had appropriate material for review. Of the 65 cases, only 11 were correctly identified as MGA, while others were misdiagnosed as MGA instead of adenosis, underlining the difficulty that MGA poses for appropriate diagnosis. According to Khalifeh et al., three variants of MGA can be identified: uncomplicated MGA, MGA with atypia (AMGA), and Breast carcinoma-associated microglandular adenosis (BCMGA). There is
Clinical observations have described excised MGA lesions as hardened, gray-white fatty breast tissue lacking uniform borders\(^{16}\) or, alternatively, as firm, rubbery, and nonencapsulated.\(^2\) Histologic descriptions of MGA showcase disorganized, small, uniformly sized glands infiltrating dense, hypocellular, or adipose breast tissue.\(^{21}\) The cells in MGA exhibit a singular layer of cuboidal epithelial cells with clear, foamy, granulated, or vacuolated cytoplasm containing eosinophilic secretions.\(^1\) Histology studies of these secretions show stain positive for PAS and mucicarmine, indicating their glycogen-rich nature.\(^{21}\)

Unlike other forms of adenosis, MGA lacks cytoplasmic protrusions and apical snouts, and lacks myoepithelial cells, causing a lack of expression of p63 and calponin. This leads to potential confusion with invasive breast carcinomas such as tubular carcinoma. IHC studies have shown MGA lesions to be immunoreactive to pan-cytokeratin and s100 proteins and positively staining for cathepsin-D and cytokeratins such as CK8/18.\(^1\) These lesions do not express epithelial membrane antigen, gross cystic disease fluid protein 15, and highly implicated biomarkers seen in malignant breast lesions like estrogen receptor, progesterone receptor, and human epidermal growth factor 2.\(^{21}\) Carcinomas that can arise from the malignant transformation of microglandular adenosis also share these immunohistological characteristics, further complicating the diagnosis.\(^9\) However, microglandular adenosis lacks the stromal desmoplastic reactions typically seen in invasive carcinomas. The glands are encased in a thickened basement membrane that stains positive for laminin and type IV collagen.\(^1\) Notably, open tubules within MGA are often noncompressible, with lumens filled with eosinophilic and occasionally calcified secretions. Nuclei typically exhibit well-defined features with minimal active mitotic figures.\(^{21}\) These defining characteristics serve to differentiate MGA from more invasive lesions. In instances where significant atypia manifests, classification shifts to atypical microglandular adenosis; our case is characterized by features such as increased active mitotic figures, glandular budding, luminal bridging, and loss of basement membranes indicating a transition from a benign breast lesion to an atypical lesion and potentially malignant lesion.

Although microglandular adenosis has relatively standard management and treatment, the prognosis can be unique, with several points of interest.\(^{11}\) Several factors set it apart from other, similar benign masses. Microglandular adenosis is considered a benign lesion, and it cannot metastasize. Therefore, the prognosis for patients with MGA is generally good. The biggest challenge with MGA is its histological similarity to invasive carcinoma. There have been cases where MGA was misdiagnosed as carcinoma, leading to unnecessary treatment interventions. However, with advancements in diagnostic techniques, such as immunohistochemistry...
and molecular studies, the accuracy of diagnosis has improved, reducing the likelihood of misdiagnosis.\(^1\)

Although MGA itself is benign, studies have suggested an association between MGA and concurrent or subsequent development of carcinoma, particularly triple-negative breast cancer.\(^3\) Therefore, patients diagnosed with MGA may require close monitoring through regular clinical examinations and imaging studies to detect any potential malignant transformation or the development of separate carcinomas. Although the prognosis is generally good, it can vary based on several factors. Prognostic factors for MGA include the size and extent of the lesion, the presence of atypia or mitotic activity, and the presence of concurrent malignancy. Lesions with atypia or extensive involvement may have a slightly higher risk of concurrent or subsequent carcinoma.\(^2\) Our case with the diagnosis of AMGA was followed for 28 months with no evidence of recurrence or malignant transformation. While MGA itself is benign, the diagnosis and management process can still cause significant psychological distress for patients, as with any cancer diagnosis. Providing adequate support and education to patients about the nature of MGA and its prognosis is essential for alleviating anxiety and ensuring informed decision-making. Despite advancements in understanding MGA, there are still gaps in knowledge regarding its pathogenesis, risk factors for malignant transformation, and optimal management strategies. Further studies are encouraged to elucidate these aspects and improve patient outcomes.

Studies have established standard treatment for uncomplicated cases and dictated conditions for alternate or additional treatments. The current treatment of MGA is total excision. An excisional biopsy is indicated if a needle core biopsy demonstrates MGA on histopathologic analysis and excisional samples should be thoroughly tested to rule out any features of malignancy.\(^2\) In uncomplicated cases, clinical follow-up should occur following total excision to screen for recurrence, as mentioned above. Treatment of more complicated cases requires additional measures. If worrisome features are present, such as epithelial proliferation or cell atypia, wide excision ought to be considered.\(^3\) A necessary additional measure needed in cases of AMGA is an assessment of surgical margins for remaining atypia. Due to this atypia, histological evaluation of AGMA can be difficult. The current best practice involves using an S100 histopathologic stain to delineate resection margins. MIB-1 stain is also used to recognize atypia and obtain the proliferation index.\(^23,24\) If margins are found to contain additional atypia, reexcision is recommended.\(^22\) Love et al. detailed a notable case of carcinoma emerging in a patient who had a resection of MGA 10 years prior, demonstrating the significance of completely excising the lesion at the time of treatment. This total resection is fundamental to reducing the risk of recurrent carcinoma emerging from remaining indolent MGA. Antineoplastic medical therapy and radiotherapy are not indicated for MGA or AMGA.\(^25\)

This case report is uncommon given the concurrent presentation of MGA in addition to glandular atypia (AMGA), combined with an undetermined radiological appearance that complicated the diagnostic process. AMGA is rare and has been documented to increase the complexity of accurate diagnosis and management. Studies have shown that AMGA is sometimes mistaken for invasive carcinoma because it grows quickly and shares some histopathological features with malignant breast diseases.\(^25\) This case underscores the critical need to recognize the subtle histological features of AMGA, thus avoiding overtreatment and guiding appropriate clinical management. By providing a detailed analysis of this case’s clinical and pathological features, this report aims to enhance understanding and awareness of AMGA among clinicians, radiologists, and pathologists, thereby facilitating more accurate diagnosis and optimal management strategies. The insights derived from this case are grounded in a thorough review of current literature, emphasizing the clinical implications of distinguishing MGA from malignant breast lesions.

Microglandular adenosis (MGA) is a rare benign yet non-obligate precursor to triple-negative breast carcinoma. However, recent molecular studies show that MGA may progress to luminal and other types of breast cancer in addition to TNBC, such as hormone-positive (ER+, PR+) breast cancers. MGA is a rare lesion, and awareness of this tumor is required for its inclusion in the clinical, pathological, and radiological diagnoses.

### Figures:

![Microscopic examination of the tumor mass](image)

1A: MGA, Low-power view showing randomly spaced, uniformly sized, spherical, open glands with eosinophilic secretions. The glands appeared to infiltrate the breast fatty tissue, but there is no dense stromal reaction to the infiltrating glands (H&E stain X20)

1B: MGA, High-power view showing the glands are lined-up with a single layer of cuboidal epithelial cells with clear, foamy, granulated,
and some vacuolated cytoplasm containing eosinophilic secretions (H&E stain X40)
1C: AMGA, low-power view showing glandular crowding, budding, luminal bridging, and loss of basement membranes (H&E stain X20)
1D: AMGA, high power view highlighting nuclear atypia and mild pleomorphism (H&E stain X40)

Figure-2: Immunohistochemistry studies of the tumor mass
2A: Tumor cells positive for S-100
2B: Tumor cells negative for Estrogen (ER)
2C: Tumor cells negative for smooth muscle myosin-heavy chain (SMM-HC)
2D: Tumor cells negative for P63

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*Corresponding author: Jessica Jahoda*, MD Candidate, Research Writing & Publication (RWP) LLC, NY, USA, Email: jessicajahoda94@gmail.com

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