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Idiopathic Granulomatous Mastitis: Diagnosis and Histopathologic Features

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ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is a rare benign inflammatory breast condition, mostly affecting women of reproductive age within a few years of pregnancy. Due to diverse clinical and radiologic features, IGM can mimic a vast spectrum of breast conditions. Therefore, histological findings are one of the most essential bases of diagnosis.

Methods: A literature search was performed to review the characteristics of IGM with an emphasis on histopathological features in English sources from 2010 to 2022. The key words used for PubMed database search were "breast", "granulomatous mastitis", "histopathology", and "pathology."

Results: In total, 192 articles were retrieved, from which 38 most relevant manuscripts were selected for this review article.

Conclusion: The diagnosis of IGM depends on clinical, radiologic, and pathologic findings. Palpable mass is the most frequent complaint**.** An irregular hypoechoic mass with varying degrees of posterior phenomena is the most common sonographic finding. Histologically, IGM is characterized by a non-caseating lobulocentric granulomatous inflammation; composed of tight aggregates of epithelioid histiocytes with or without multinucleated giant cells. At times, the presence of cystic empty vacuoles lined by neutrophils is noted that is commonly associated with cystic neutrophilic granulomatous mastitis (CNGM), a variant of IGM. Atypical findings for IGM includes: The presence of atypia and/or malignancy, caseous necrosis, marked eosinophilic infiltration, absence of granulomatous inflammation, etc.

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare benign inflammatory breast condition, mostly affecting women of reproductive age within a few years of pregnancy.[1] The most frequent clinical presentation is a palpable breast mass; other symptoms include tenderness, induration, erythema, or abscess formation.[2,3] Ultrasound findings are nonspecific and vary from structural distortion and edema to axillary lymph nodes enlargement.[4] However, an irregular hypoechoic mass with varying degrees of posterior phenomena is the most common sonographic finding.[5]

Due to diverse clinical and radiologic features, IGM can mimic a vast spectrum of breast conditions including inflammatory breast carcinoma or

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infections, which often leads to misdiagnosis and delayed treatment.[6,7] Therefore, IGM remains a diagnosis of exclusion that should be supported by histopathological findings.[8] Histologically, it is characterized by the presence of mostly lobulocentric non-caseous granuloma composed of epithelioid histiocytes, multinucleated giant cells, and lymphocytes associated with neutrophilic aggregate.[9]

Currently, there is no optimal treatment for IGM. Mastectomy, surgical excision, wound drainage, steroid therapy, antibiotics, and even expectant management are all considered as possible treatment approaches; however, recurrence rate may be as high as 50% even after surgical excision.[10-12]

We aim to review essential histopathologic features of IGM along with less debated pathological findings to provide a comprehensive pathological manuscript on this condition. Furthermore, we point out unusual findings of IGM to facilitate avoiding diagnostic pitfalls and propose a practical approach for the diagnosis of IGM.

METHODS AND RESULTS

In the current study, a literature search was performed to review the characteristics of IGM with an emphasis on histopathological features in English sources from 2010 to 2022. The key words used for PubMed database search were "breast", "granulomatous mastitis", "histopathology", and "pathology."

In total, 192 articles were retrieved in the initial pursuit. The articles focusing on only therapeutic approaches, or clinical and radiological features without any histopathological description were excluded. Also, studies pertaining to the specific cause of granulomatous mastitis were excluded. Finally, 38 most relevant manuscripts were selected for the purpose of this review article.

DISCUSSION

IGM is widely reported in Asia and the Middle East.[5] Due to its rather high frequency in this geographic area including Iran, this review aims to share our experiences regarding the histopathologic features of this disorder.

Clinicoradiologic presentation

About half of the patients are in the 30-40 age group and only a minority of patients are older than 50 years. The history of breastfeeding in recent years has been reported in approximately 25% of the cases (Unpublished observation).

A palpable mass is the most frequent complaint in IGM, sometimes accompanied by nipple retraction and inflammatory symptoms such as pain, skin erythema, or stiffness.[13]

The disease mostly affects one breast in any quadrant, but the involvement of upper outer quadrant is slightly more common.[14]

Although not pathognomonic, asymmetric ill-defined increased density on mammography, and a heterogenous echogenic irregular mass with areas of tubular configuration on sonography are the most common radiologic features.[15]

Pathogenesis of IGM

The pathogenesis of IGM is yet to be known, but several possible etiologies have been considered including hypersensitivity to extravasated lactation products, local breast trauma, undetected infection, and autoimmune processes.[3,16-18] Moreover, breastfeeding, pregnancy, hyperprolactinemia, smoking, oral contraceptives, diabetes mellitus, and antitrypsin deficiency are suggested as possible contributing factors. Not only can hyperprolactinemia trigger IGM, but it may also prolong the course of the disease and increase the risk of recurrence.[19,20] Although galactosis is a key factor associated with IGM, it is not essential for pathogenesis as the disease also occurs in men and postmenopausal women.[21-23]

Typical histopathologic features

The diagnosis of IGM relies heavily on histopathological features. Typically, it is characterized by a non-caseating lobulocentric granulomatous inflammation, composed of tight aggregates of epithelioid histiocytes with or without multinucleated giant cells. Generally, the pathologic triad of IGM includes the presence of granuloma, lonulocentric inflammation and neutrophilic infiltration (Figures 1 and 2). However, the presence of well-formed granulomas is not mandatory, and loose aggregates of histiocytes (i.e., poorly formed granulomas) may be observed in some cases.[5,24]

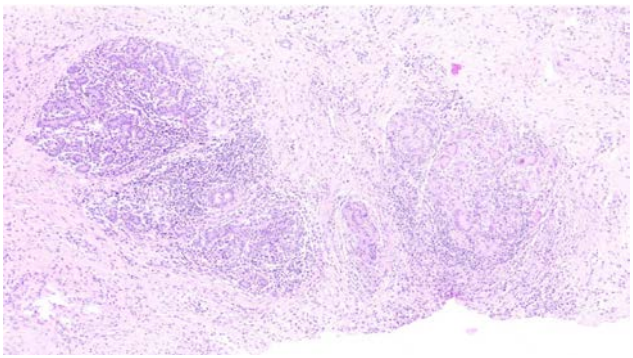

Figure 1. This low power view depicts the lobulocentric nature of the inflammation. The granulomatous inflammation is seen in the right side of the image. H&E, 100x.

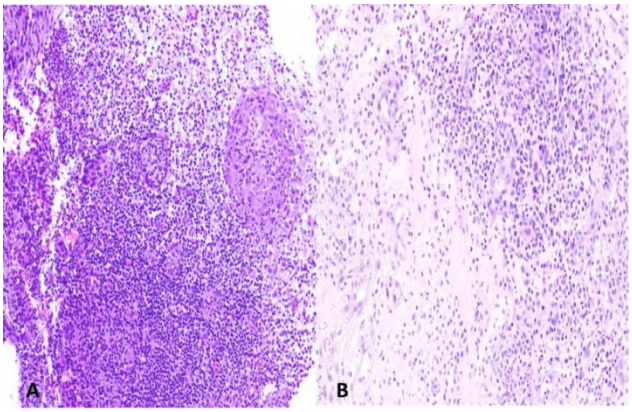

Figure 2. A well-formed granuloma and a lobulocentric inflammation are depicted in this photomicrograph. H&E, 200x. B. This image shows the lobulocentric mixed inflammation on the right side and granulation tissue formation on the left side of the image. H&E, 400x.

The giant cells include a mixture of foreign body and Langhans types with the preponderance of foreign body type giant cells in a brief unpublished study performed in our center (Figure 3).[25,26]

Additionally, acute and chronic inflammatory cells and neutrophilic microabscesses are often seen. (Figures 4.A) Other less common features include fat necrosis, granulation tissue formation, and fibrosis (Figures 5).[27]

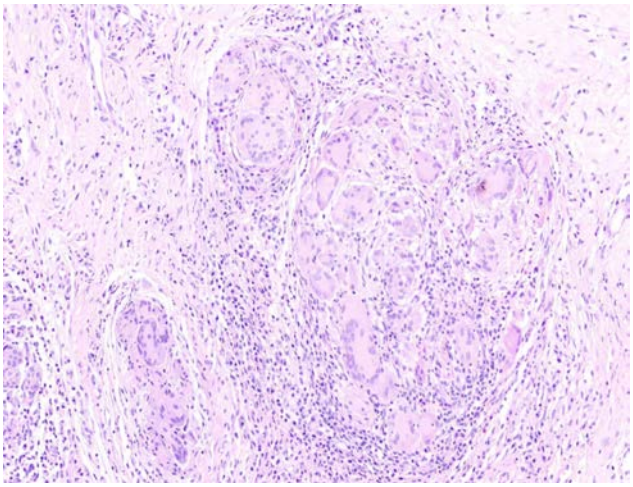

Figure 3. Higher power view of the granulomatous inflammation. Note the mixed population of giant cells including both foreign body and Langhans types. H&E, 400x.

Another peculiar feature is the presence of empty cystic spaces mostly surrounded by varying numbers of neutrophils, histiocytes, and lymphocytes.[28] These empty spaces are commonly associated with cystic neutrophilic granulomatous mastitis (CNGM), a variant of IGM.[29]

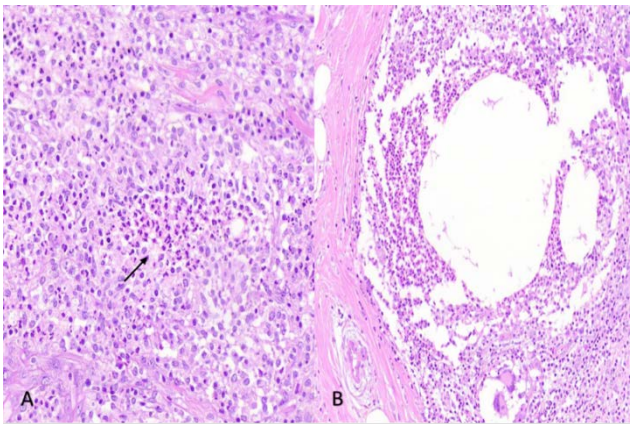

Figure 4. A. Note the neutrophilic microabscess in the center of this photomicrograph (arrow head). H&E, 400x, B. Note the cystic neutrophilic granulomatous mastitis, H&E, 200x.

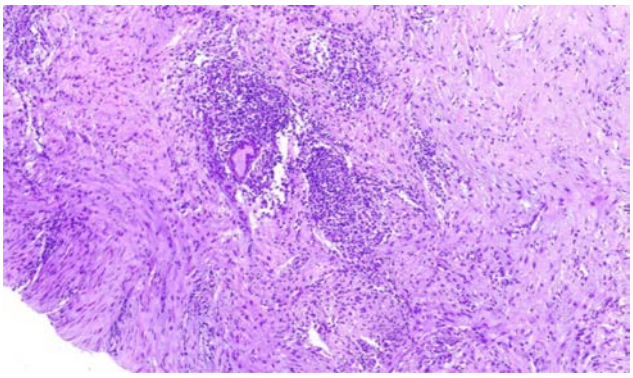

Figure 5. Marked fibrosis and chronic inflammation are shown in this image.

Lobulocentricity is very important for the correct diagnosis; however, lobular architecture is at times obliterated due to the confluence of the inflammation, making identification of its lobulocentric nature challenging. Paying attention to the less inflamed areas of the specimen may be helpful in difficult cases. Therefore, we recommend searching for unequivocal evidence of lobulocentricity in the specimen by preparing multiple step sections and total submission of the specimen in difficult situations.

Cystic neutrophilic granulomatous mastitis (CNGM)

The presence of cystic vacuoles lined by neutrophils is seen in some cases of IGM. Renshaw *et al*. called this odd pattern "Cystic neutrophilic granulomatous mastitis".[30] Some authors consider this entity a variant of IGM.[30-32] The characteristic morphologic feature of CNGM is a suppurative lipogranuloma with empty spaces surrounded by successive layers of neutrophils and epithelioid histiocytes (see Figure 4.B).[33,34] The most distinctive feature of CNGM is the identification of a lipophilic rod-shaped gram-positive bacillus from the Corynebacterium genus.[12] The most common isolates

are C. kroppenstedtii, followed by C. amycolatum, and C. tuberculostearicum.[35-37]

The bacillary microorganisms can be identified in the empty spaces by the high-power examination of the lesion, though negative cases are common due to the scarcity of bacteria and poor Gram staining.[38] According to Paviour *et al*., Corynebacterium could be proposed as a pathogenetic factor in IGM. In their study, the bacteria were found deep in the breast tissue surrounded by granulomatous inflammation in early stages.[39]

Atypical for IGM

Some histopathologic features are alien to IGM. The pathologist should diligently search for these changes if she/he is to avoid a wrong diagnosis. These changes can be summarized as follows:

The presence of atypia and/or malignancy is of great significance. Sometimes, invasive or in situ carcinomas may elicit a great deal of inflammation that may look like IGM superficially. There are also reports of coincidence of malignancy and IGM.[40] Özsen *et al*. reported a case of IGM resistant to therapy, where trucut biopsy revealed a ductal carcinoma in situ component.[41] Mazlan *et al*. reported a case of recurrent IGM that developed progressive visual loss. Further evaluation revealed distant metastasis of right breast invasive ductal carcinoma to the orbit. Additionally, synchronous cases of IGM and invasive breast cancer have been reported in contralateral breasts.[42,43]

The absence of granulomatous inflammation is very important. Granulomatous inflammation is a major component of IGM. If no granuloma is identified after complete submission of the specimen and multiple step sections, the pathologist should think of alternative diagnoses including infections and abscess formation. Nonetheless, it should be noted that the absence of granulomas does not exclude the possibility of IGM.[27]

Identifying an infectious agents (other than Corynebacterium species) within the granulomatous inflammation including acid-fast bacilli, fungal elements, or parasites is also of importance. The most common cause of infectious granulomatous mastitis is tuberculosis.[44] The presence of caseous necrosis is suggestive of tuberculosis. Moreover, tuberculous mastitis prominently involves the ductal structures.[6,45,46]

Marked eosinophilic infiltration is often suggestive of fungal or parasitic infestations. Also, eosinophilic infiltration within vessel walls and breast tissue can be seen in Eosinophilic Granulomatosis with Polyangiitis.[47,48]

The presence of ectatic ducts surrounded by lymphocytic and histiocytic infiltration is suggestive of mammary duct ectasia (MDE). Jiang *et al*. conducted a study to compare features of IGM with those of MDE. They reported a higher rate of granuloma, multinucleated giant cells, and microabscess formation in IGM within lobules, whereas ductal and periductal inflammation with intraductal foam cells were more common in MDE.[49]

Lobulocentric lymphocytic infiltration is suggestive of diabetic lymphocytic mastitis also known as diabetic mastopathy. It is often associated with insulin dependent Type 1 diabetes, microscopically showing keloidal stromal fibrosis, epithelioid myofibroblasts, lobular atrophy, and perivascular/ perilobular/periductal lymphocytic infiltration.[47]

Extensive necrosis is suggestive of vasculitis. In these cases, granulomas are accompanied by small-sized to medium-sized vasculitis, highlighted by elastic stains. Serologic investigations and rheumatologic consultation are recommended for excluding Wegner's granulomatosis, polyarteritis nodosa, and other collagen vascular diseases.[47]

Fat necrosis, identification of foreign bodies, and hemosiderin deposition are suggestive of traumatic injury.[50] Also, naked well-formed granulomas without accompanying neutrophilic infiltration or necrosis are in favor of sarcoidosis.[51,52]

Diagnostic approach to IGM

The diagnosis of IGM is based on the triad of clinical presentation, radiologic findings, and histopathologic changes along with the exclusion of specific causes of granulomatous mastitis.

Core needle biopsy is the best method for obtaining sufficient tissue with a success rate of 95% in some studies.[24,53,54]

Still, even with typical histopathologic and radiologic findings, other causes of granulomatous inflammation, particularly infections, should be excluded clinically. If histopathologic findings are atypical for IGM, further investigations based on the histopathologic impression are of vital importance. If clinicoradiologic findings are discordant with the histopathologic diagnosis of IGM, re-biopsy is strongly advocated regardless of histopathologic changes. The diagnostic approach is summarized in Figure 6.

CONCLUSION

The diagnosis of IGM depends on clinical, radiologic, and pathologic findings. Other etiologies of granulomatous inflammation including infectious agents should be excluded by further laboratory investigations including the culture and molecular studies of the specimen for microbial agents.

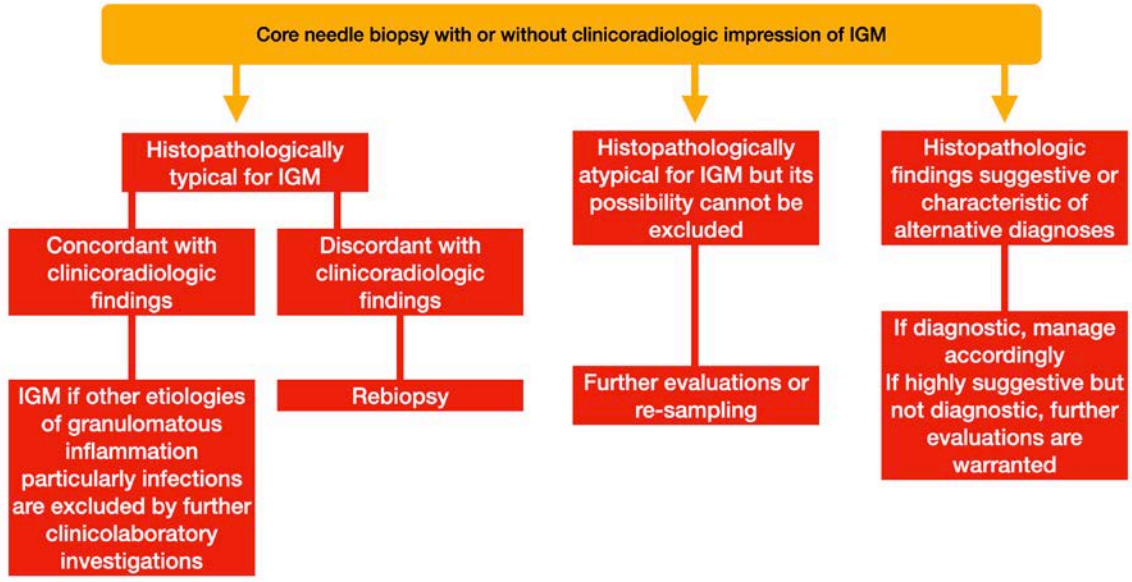

Figure 6. Our proposed diagnostic approach for IGM

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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