REVIEW

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Idiopathic Granulomatous Mastitis: Overview and Imaging Findings

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Abstract

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory breast disease characterized by non-caseating granulomas in the lobules of breast tissue. IGM primarily affects women of childbearing age. The actual prevalence of IGM is unknown although it is considered rare. Although the exact cause remains unclear, various triggers, such as autoimmunity, hormonal factors, and infectious agents, are believed to play a role in its pathophysiology. Imaging techniques, particularly ultrasound (US) and mammography, play vital roles in the preliminary diagnosis. The most common imaging findings are focal asymmetry on mammography and hypoechoic lesions that tend to coalesce and form tubular extensions on US. Advanced imaging techniques, including elastography and magnetic resonance imaging, can aid in diagnosis, although none of these findings are pathognomonic, necessitating histopathological evaluation for definitive diagnosis. Unlike infectious mastitis, antibiotics are not recommended for the treatment of IGM unless there is an accompanying bacterial infection. IGM should be considered in patients with mastitis that does not resolve despite prolonged antibiotic treatment. Corticosteroids are an effective first-line therapy for patients with histopathologically proven symptomatic IGM. Accurate diagnosis and treatment are crucial because of the potential for IGM findings to be mistaken for malignancy. This review discusses the general characteristics and imaging findings of IGM based on the current literature.

Keywords: Idiopathic granulomatous mastitis, ultrasound, mammography, magnetic resonance imaging, breast elastography, differential diagnosis

Introduction

Idiopathic granulomatous mastitis (IGM), also known as non-puerperal mastitis or granulomatous lobular mastitis, was first described in 1972 by Kessler and Wolloch.[1] IGM is a rare, chronic, inflammatory benign breast disease. This condition predominantly affects women of childbearing age, particularly in developing countries, and often occurs postpartum or during lactation.[2-4] Although the etiology of IGM remains unclear, it has been suggested to be associated with autoimmune processes.[2,5,6]

Clinically, IGM presents with symptoms such as pain, inflammation, erythema, and a palpable mass, with the latter being the most common. The clinical and radiological features of IGM often overlap with those of breast cancer and various benign inflammatory breast diseases, leading to frequent misdiagnosis and delayed treatment.

Ultrasound (US) and mammography play significant roles in the diagnosis of IGM. However, due to the non-specific nature of imaging findings, definitive diagnosis generally requires histopathological evaluation and exclusion of other conditions.[7]

There are various treatment options for IGM, including surgical resection, abscess drainage, steroids, methotrexate, and watchful waiting. However, no consensus has been established on the optimal treatment approach, which is often based on clinical experience and tailored to the patient and the severity of the disease.[8]

This review discusses imaging findings, pathophysiology, clinical presentation, and treatment approaches for IGM based on the current literature.

Etiology and Pathophysiology

In the pathophysiology of IGM, it is proposed that damage occurs in the ductal epithelial cells of the breast for various reasons. This damage leads to the leakage of luminal secretions into the lobular stroma of the breast, which subsequently triggers a local inflammatory response induced by the migration of macrophages and lymphocytes to the area, followed by the formation of a granulomatous reaction.[9]

Since the exact cause of IGM remains unclear, most cases are termed "idiopathic". However, it is believed that certain "environmental stimuli" can trigger an inflammatory granulomatous reaction, primarily in genetically predisposed individuals. There are three hypotheses that are thought to be responsible for the pathogenesis of IGM: autoimmunity, infection, and hormonal disorders.[10] Additionally, alpha-1 antitrypsin deficiency, oral contraceptives (OCs), smoking, breastfeeding, and pregnancy are considered potential predisposing factors. The presence

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of multiple predisposing factors is believed to further exacerbate the disease.[8]

The effectiveness of immunomodulatory drugs, such as steroids and methotrexate, in treating IGM supports the autoimmune theory.[11,12] Furthermore, some studies have found positive anti-nuclear antibodies, rheumatoid factor, and elevated serum levels of interleukin (IL)-17, IL-22, and IL-23 in patients with IGM.[13,14]

Another hypothesis regarding the pathogenesis of IGM is infectious processes. Corynebacterium bacteria have been isolated from IGM cases, suggesting a possible role in the disease.[15] However, since these bacteria are also part of the normal skin flora of the breast, it remains debated whether the bacteria found in samples from IGM cases are contaminants or pathogens.[8,16]

Hormonal factors, such as hyperprolactinemia, are believed to be responsible for IGM recurrence and prolonged disease duration.[2] Pituitary adenomas and selective serotonin reuptake inhibitors that increase prolactin levels have also been implicated. Although it has been proposed that elevated prolactin levels lead to increased milk secretion and ductal damage, resulting in the leakage of milk secretions into the stroma and subsequent inflammatory reactions, this theory has not been definitively proven.[17,18]

IGM typically appears within 5 years postpartum and is associated with breastfeeding, with an average onset age of 33-38 years.[19]

Gurleyik et al.[21] reported that 15 out of 19 IGM patients had a history of breastfeeding, while Azizi et al.[20] found that 90.7% of 474 IGM patients had a history of pregnancy, and 82.7% of these patients had breastfed. Although pregnancy, childbirth, and breastfeeding are strongly associated with IGM, the disease is also observed in men and women aged >80 years, indicating that these factors are not fundamental pathogenic factors.[8]

OCs, similar to hyperprolactinemia, have been suggested as potential factors for IGM pathology because of their role in increasing breast secretion. Some studies have found varying percentages (21-42%) of OC use among IGM cases[21,22], whereas other studies have not demonstrated a significant relationship.[23]

In our opinion, since IGM is more frequently observed in developing countries, studies with large sample sizes are often conducted in such populations. However, the lower rates of smoking and OC use in these countries compared with the Western countries may lead to misleading results regarding potential factors.

Clinical Findings

IGM most commonly presents in women aged 30-45 years with a unilateral, palpable breast mass of varying sizes (1-20 cm). It can occur in any quadrant of the breast, but it is most frequently reported in the upper outer quadrants.[24] The palpable mass may be accompanied by skin manifestations such as erythema, nipple retraction, and a peau d'orange appearance. In chronic and severe cases, abscess formation, ulcerative appearance of the skin, and purulent discharge through sinus tracts extending to the skin may occur.[8] Additionally, ipsilateral axillary lymphadenopathy may be present in some cases.

Due to its presentation with a breast mass and skin changes, the differential diagnosis of IGM can be challenging, even with the use of mammography, US, magnetic resonance imaging (MRI), and other imaging modalities, to distinguish it from inflammatory breast cancer (IBC). Furthermore, although rare, breast tuberculosis should be considered in the differential diagnosis. However, the presence of concomitant pulmonary findings in tuberculosis, the demonstration of caseous necrosis on histopathological examination, and the involvement of breast ducts can help rule out IGM.[25] Ultimately, because IGM is rare and its clinical findings are not specific, imaging findings and histopathological examination are required for diagnosis.

Imaging Findings

In the presence of a palpable breast mass, as observed in IGM, the accepted approach is to perform US for patients under 40 years of age and mammography for patients over 40 years of age.[19] Additionally, advanced imaging techniques, such as elastography and tomosynthesis, are used in clinical practice. When US and mammography are insufficient, MRI plays a significant role in demonstrating disease extent and detecting active inflamed tissue remnants that may be obscured by edematous tissue.

Mammography

Various mammographic findings of IGM have been described, but none are pathognomonic. A review of the literature revealed that the most commonly encountered mammographic findings are irregular and poorly defined masses with focal asymmetry (Figure 1). However, it should be noted that no pathology may be detected on mammography in patients with dense breast tissue or mild symptoms in the initial stage.[19,26,27]

Additional mammographic findings included axillary lymphadenopathy, focal skin thickening or edema, and nipple retraction (Figure 2). Similar findings were observed in IBC; however, in cancer, edema involves a larger portion of the skin, whereas in IGM, focal edema affects a smaller area of the skin.[28]

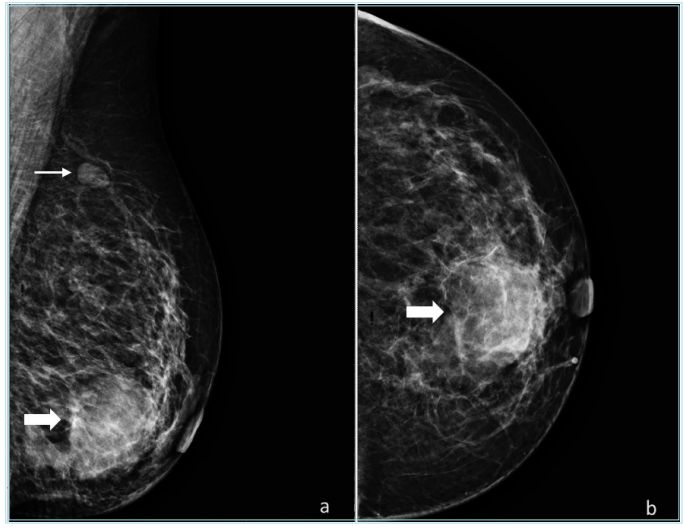

Figure 1. In the mediolateraloblique (MLO) (a) and craniocaudal (b) mammographic images of a 45-year-old female patient presenting with palpable mass and breast tenderness, an irregularly and poorly defined nodular opacity (arrows) is observed in the lower central quadrant. Additionally, the MLO view reveals a nodular appearance of a reactive intramammary lymph node (thin arrow) in the upper half (correlated with ultrasound). Pathology results reported "granulomatous mastitis"

(From the archives of Prof. Dr. Irmak Durur Subasi)

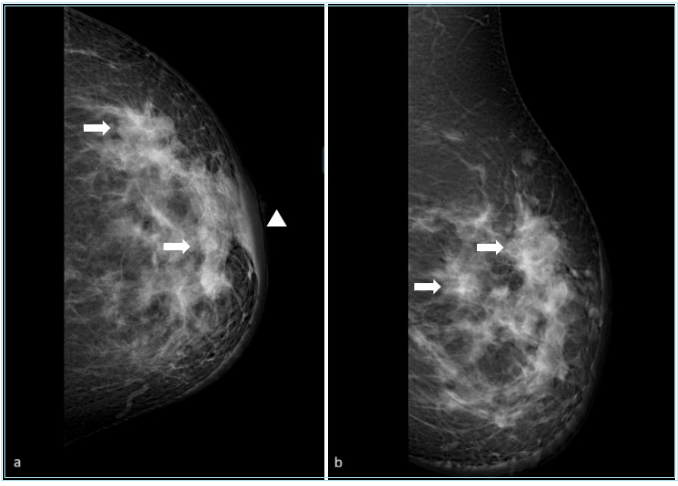

Figure 2. In the left breast craniocaudal (a) and mediolateraloblique (b) mammograms of a 39-year-old female patient, focal asymmetries are observed, with several irregularly defined nodular densities tending to coalesce, the largest in the upper outer quadrant (arrows). Associated skin thickening/edema around the areola is also present (arrowhead). Core needle biopsy pathology results indicated "granulomatous lobular mastitis"

Calcifications are not typical mammographic findings in IGM. Fazzio et al.[29] proposed that calcifications might be a rare finding in granulomatous mastitis, based on a case with segmental coarse heterogeneous calcifications. Additionally, there have been reports in the literature in which microcalcifications associated with synchronous breast cancer were masked during the active phase of IGM but were detected in follow-up mammograms after treatment. These findings suggest that post-treatment mammography is beneficial in avoiding missing synchronous cancer lesions once breast pain or tenderness subsides.[30,31]

In conclusion, although mammographic findings may raise suspicion of IGM, no pathognomonic features allow for a definitive diagnosis. Correlations with other radiologic modalities and histopathologic sampling are necessary for a definitive diagnosis.

Ultrasound

Regardless of age, US is the primary imaging modality for patients with symptoms of mastitis. US is also frequently used in IGM for image-guided biopsies and intralesional steroid treatment because of its nonradiative nature.

Although the sonographic appearance of IGM varies greatly, the most frequently reported finding is irregularly shaped hypoechoic lesions or masses with or without tubular extensions. The tubular extension and coalescing tendency of the lesions describe the reticular appearance of the disease spreading around the lobules.[7,27,32,33] The orientation of lesions is almost always parallel to the skin.[33] On Doppler US, the lesions and surrounding tissues exhibited hypervascular characteristics (Figure 3).[29,34] In the advanced stages of the disease, breast abscesses can develop, with reported prevalence in the literature ranging from 6.6% to 54.0%.[29,32,35]

Auxiliary US findings for the diagnosis of IGM include skin thickening and subcutaneous fat tissue edema, increased echogenicity of subcutaneous fat tissue secondary to inflammation, and reactive axillary lymphadenopathy with preserved fatty hilum and thick cortex. The frequency of these findings varies across studies.[12,19,33,35,36]

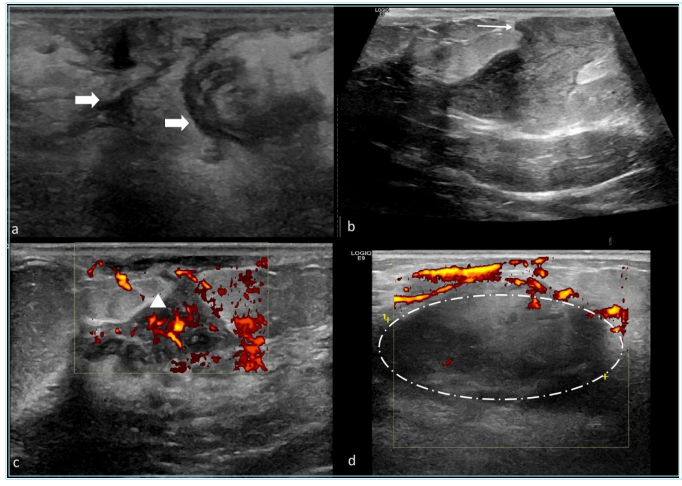

Figure 3. Ultrasonographic images from three different patients diagnosed with idiopathic granulamatous mastitis. The first image (a) shows irregular hypoechoic lesions interconnected by tubular extensions (arrows) and increased echogenicity of fat tissue due to inflammation. The images (b) and (c) display polygonal-shaped irregular hypoechoic lesions with vascularization on doppler imaging (arrowhead), extending towards the skin (thin arrow). The image (d) shows a hypoechoic round abscess focus (circled) with peripheral vascularization in the advanced stages of the disease

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Elastography

Elastography is an innovative complementary imaging technology that enhances the diagnostic capabilities of B-mode US by evaluating tissue stiffness. There are two primary types of elastography used to assess breast lesions: shear wave elastography (SWE) and strain elastography. Strain elastography is operator-dependent, whereas SWE, which uses focused radiation forces without manual compression, is independent of the operator. Using SWE, color-coded maps (elastograms) based on tissue stiffness are created, allowing for semi-quantitative measurements.

Studies have shown that SWE is effective in distinguishing benign from malignant breast lesions and can improve the specificity of traditional US when using the Breast Imaging Reporting and Data System (BIRADS) criteria. Elastography plays a crucial role in distinguishing BIRADS 3 from BIRADS 4A lesions in diagnosis.[37] While clinicians often use palpation to understand the elasticity of pathological tissues or masses, sonoelastography provides a more objective method, enabling more sensitive and specific differentiation between benign and malignant breast lesions based on stiffness.[38]

Various studies have investigated its efficacy in differentiating IGM from breast malignancies.[39,40] A recent study by Toprak et al.[41] explored the qualitative and quantitative roles of SWE in distinguishing IGM from invasive ductal carcinoma, obtaining 89% sensitivity and 84% specificity. Another study by Durur-Karakaya et al.[40] found that qualitative and semiquantitative elastography parameters evaluated in all IGM cases were consistent with the benign criteria. They found that sonoelastography revealed low ES and SR values and equal ED for IGM. Because these are all features of benign breast lesions, sonoelastography may be a valuable technique for the diagnosis of IGM (Figure 4).

However, Aslan et al.[42] measured the stiffness of lesions in IGM cases before and after treatment and found no significant difference. Additionally, Ece et al.[43] evaluated the feasibility of using elastography

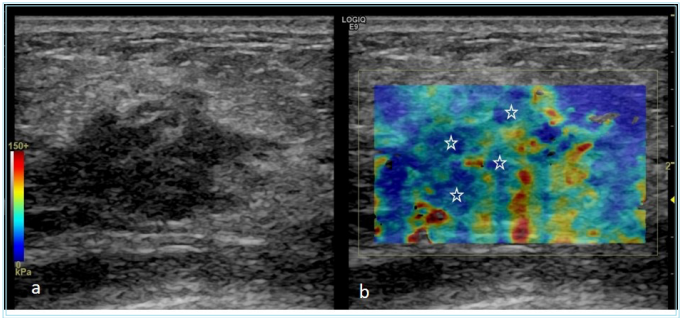

Figure 4. In a patient diagnosed with idiopathic granulamatous mastitis, a hypoechoic patchy area is observed on gray-scale ultrasound (a), and free-hand elastography reveals that the lesion predominantly consists of soft areas coded in blue (stars). In contrast, malignant masses typically appear as stiffer structures on elastography

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to adjust corticosteroid doses in the treatment of IGM, noting that the use of SWE may allow for lower corticosteroid dosages. More studies are needed to demonstrate the value of SWE in predicting clinical response to IGM.

Magnetic Resonance Imaging

MRI is typically used in specific scenarios where US and mammography are insufficient for decision-making, to determine lesion extent, assist with biopsy, and to evaluate auxiliary extramammary findings. Additionally, MRI is useful for assessing suspicious residual inflammatory areas. Although MRI is less frequently used compared with US and mammography, its sensitivity and high positive predictive value make it a valuable tool.[12,27,29,30,44,45]

IGM MRI findings, like those on US and mammography findings, vary significantly. When evaluating the MRI characteristics of breast lesions, the edge features of the lesions are of primary importance. Although malignant breast lesions typically have spiculated and irregular edges, benign breast lesions usually have smooth or lobulated edges. IGM is an exception, as its lesion contours can be smooth, lobulated, or spiculated despite being benign, necessitating advanced imaging with contrast-enhanced MRI.[46-48]

In MRI, IGM shows focal or diffuse asymmetric signal enhancement and contrast uptake. The most common pattern observed is hyperintense signal on T2-weighted images (WI), hypointense signal on T1WI, with segmental heterogeneity and irregular contrast-enhancing lesions (Figure 5). Nodular lesions and abscesses can also be observed. The severity of the inflammatory reaction and the amount of fibrotic content in IGM vary over time, leading to different MRI findings depending on the phase. For example, aseptic abscess formation, thought to develop via an autoimmune mechanism, can be observed in a certain phase of IGM. IGM lesions show heterogeneous, diffuse, or nodular contrast enhancement patterns, and peripheral contrast enhancement is observed in abscesses (Figure 6). Although IGM lesions typically exhibit a type 1 benign contrast-enhancement pattern in post-contrast dynamic series, they have occasionally been reported to show a type 3 malignant contrast-enhancement pattern.[7,26,46,49]

In diffusion MRI, abscess foci in IGM can show diffusion restriction with low ADC values, necessitating differentiation from malignancy. In MRI spectroscopy, a choline peak is observed in malignant lesions, whereas this peak is not seen in IGM abscesses.[50] Additionally, the peripheral contrast enhancement pattern of abscesses aids in distinguishing them from malignancies.

IGM and Differential Diagnosis

IGM is challenging to diagnose due to similarities to malignancies and other inflammatory breast diseases. Definitive diagnosis is achieved through clinical history, examination findings, imaging results, and histopathological examination, making IGM a diagnosis of exclusion.

The primary diseases to consider in the differential diagnosis of IGM are IBC, infective mastitis, breast tuberculosis, diabetic fibrous mastopathy, foreign body granulomas, and sarcoidosis (Table 1).[7]

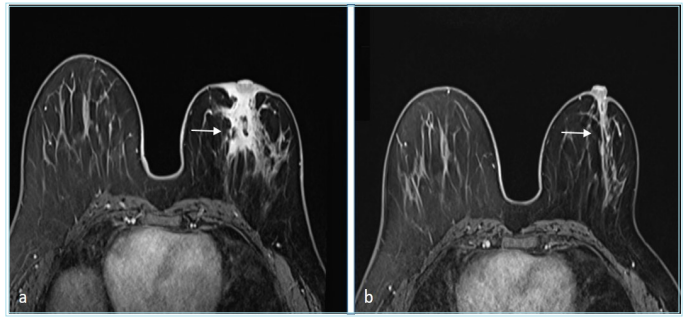

Figure 5. Post-contrast T1-weighted (T1W) breast magnetic resonance images of a 38-year-old female patient show a heterogeneous irregularly shaped area of enhancement in the right retroareolar region (a), one year after treatment follow-up images of the same patient (b), show near-complete regression of the findings (thin arrows). The pathology result confirmed "granulamatous mastitis"

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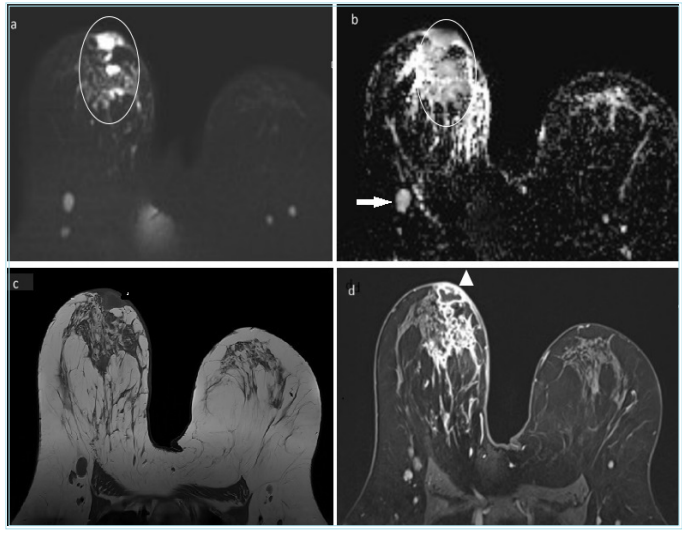

Figure 6. In the dynamic contrast-enhanced magnetic resonance images of a 30-year-old female patient, diffusion-weighted images (a) and ADC images (b) show diffusion restrictions in the abscess foci in the left breast (circled), which appear to be coalescing. In the T1W pre-contrast (c) and post-contrast series (d), peripheral enhancement is observed in the abscess foci (arrowhead), along with heterogeneously irregularly shaped enhancing lesions in other sections. Additionally, a few reactive lymph nodes are observed in the left axillary tail (arrow)

Table 1. Typical clinical and imaging-based differential diagnoses for IGM

Diagnosis	Demographics and clinical manifestations	Imaging findings	Histopathologic features
IGM	- Mainly affects premenopausal and parous women - Palpable mass, mastalgia with or without mild focal skin erythema or draining sinus, history of failed antibiotic treatments	**MG:** focal asymmetric density or irregular mass, trabecular and skin thickening. **US:** irregular hypoechoic mass with hypoechoic tubular extensions. **MRI:** heterogeneous enhancing T2-hyperintense mass and/or rim-enhancing lesions with non-mass enhancement.	- Lobulocentric non-caseating granulomas - Negative microbial staining and culture results.
IBC	- Mainly affects older women (average age, 58 years, as compared with 33 years for IGM group) - Skin erythema in at least one-third of the breast, peau d'orange, asymmetric breast engorgement, onset to manifestation of symptoms less than 3 months, axillary adenopathy in approximately 50-85% of cases.	**MG:** skin and trabecular thickening, asymmetric increased breast density with or without focal asymmetry, irregularly shaped mass, axillary adenopathy. **US:** extensive skin thickening and breast edema, dilated lymphatics, axillary adenopathy, heterogeneous parenchyma with or without suspicious or conglomerate masses. **MRI:** breast and chest wall edema, streaky T2 hyperintensity, dilated lymphatics, skin enhancement, contiguous or coalescent irregular breast masses with rapid enhancement and washout kinetics (type 3).	-Most often invasive ductal carcinoma that is poorly differentiated, with dermal lymphovascular invasion - No inflammation
Infective mastitis	- Common in females of reproductive age, but seen in persons of all ages - Non-cyclical breast pain and/or tenderness, erythema, fever with or without abscess - Clinical unresponsiveness to empiric antibiotics in the presence of positive microbial stains and/or cultures suggests an atypical or resistant organism.	**MG:** (often not performed): trabecular and skin thickening, asymmetric increasedbreast density. **US:** diffuse or focal skin thickening, inhomogeneous breast tissue with or without irregular hypoechoic mass (with or without fluid collection) (particularly lactation mastitis).	- Abundant leukocytes - Positive microbial staining and culture results, with *Staphylococcus* and *Streptococcus bacteria* often seen inspissated secretions - Atypical organisms for which additional staining is required for identification may be seen
Tuberculous mastitis	- Seen in endemic areas, high-risk populations, and persons with a history of pulmonary tuberculosis (50% of cases) - Palpable breast mass, axillary lymphadenopathy, unilateral involvement, less mastalgia compared with IGM	**MG:** findings similar to those of infectious mastitis. **US:** heterogeneous hypoechoic irregularmass, axillary lymphadenopathy with or without fluid collections.	- Caseating granulomas - Positive acid-fast or fite staining results

MG: Mamography, US: Ultrasound, MRI: Magnetic resonance imaging, IGM: Idiopatic granulamatous mastitis, IBC: Inflammatory breast cancer

IGM and Artificial Intelligence

Artificial intelligence (AI) is a modern technical discipline rooted in mathematics and computer science. It focuses on developing theories, methods, and application systems to simulate and enhance human intelligence.

Breast imaging offers distinctive features that present valuable opportunities for AI applications. The BIRADS from the American College of Radiology, with its well-established and structured lexicon, is particularly instrumental in advancing AI development and implementation. BI-RADS provides a standardized system for terminology, reporting, classification, communication, and medical auditing across mammography, breast US, and breast MRI.[51] This standardized framework is crucial for the growth and assessment of AI in breast imaging, especially by offering a predefined methodology for radiologists to interpret imaging studies and map results.[52]

There are studies in the literature that use AI to distinguish IGM from breast cancer. In a recent study, deep learning-based automatic classification systems were found to be reliable auxiliary methods for distinguishing between non-lactating mastitis and malignant breast tumors, with high sensitivity, accuracy, and specificity.[53]

Another publication demonstrated that a nomogram combining radionic and US features exhibited good diagnostic performance in distinguishing between IGM and IBC, suggesting that it could be used as a non-invasive diagnostic method.[54]

Deep Learning Radiomic Nomogram, developed based on radionic and deep learning features of US images, has been noted to have potential clinical value in effectively differentiating between mass mastitis (MM) and IBC. As the system evolves into an autonomous screening system, it is expected to improve MM diagnosis rates in rural hospitals and reduce the likelihood of incorrect treatment and overtreatment.[55]

In another publication, investigating the role of AI in distinguishing benign inflammatory breast lesions from malignant processes indicated that AI produced results comparable to radiologists' US reports for benign inflammatory diseases and demonstrated high reliability within itself. These findings suggest that AI could be considered for use in the diagnosis of granulomatous mastitis and similar inflammatory breast diseases.[56]

Treatment

There is no consensus in the literature regarding the treatment of IGM. Various treatment options are discussed, including surgical resection, steroids, methotrexate, bromocriptine, colchicine, immunosuppressive agents, antibiotics, and even conservative follow-up. Currently, treatment largely depends on the clinician's or surgeon's experience and the severity of the patient's disease.[8,57]

Although surgical excision has been widely accepted as the most common treatment for IGM, it is now considered a last resort due to the potential for recurrence, cosmetic issues, and the development of fistulas in the postoperative period.[33]

In recent years, medical treatment, particularly steroid therapy, has been recommended as first-line treatment.[58] Numerous studies in the literature have shown that oral or local (or combined) steroid therapy can alleviate preoperative symptoms and can be used as a definitive treatment option with low recurrence rates. In particular, intralesional steroid therapy has been compared with other treatment methods because it reduces the side effects associated with systemic use and provides targeted bolus therapy. It has been suggested that a quicker treatment response can be achieved, and even severe cases can be managed with monotherapy.[36,58-62] The primary adverse effect of intralesional steroid therapy is skin atrophy.

Studies by Bouton et al.[63] and Davis et al.[64] have suggested that a conservative follow-up approach should be considered, especially in mild cases. However, some studies reported frequent recurrence in these cases.[65]

Additionally, a recent study by Sarkar et al.[66] found that wide local excision with ductal excision is the best curative treatment for patients with recurrent disease who do not respond to conservative therapy.

Conclusion

IGM is a benign inflammatory breast disease characterized by non-caseating granulomas in the lobules of breast tissue. IGM most commonly affects women of childbearing age. Imaging techniques, particularly US and mammography, play crucial roles in the preliminary diagnosis. Advanced imaging techniques, including elastography and MRI, can assist in diagnosis, although none of these findings are pathognomonic, necessitating histopathological evaluation for definitive diagnosis. IGM is a rare but chronic disease that is difficult to treat and must be definitively diagnosed because of its potential to be mistaken for malignancies. Therefore, standardized diagnosis and treatment protocols based on new studies are needed.

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Note: All figures used are original, and written consent has been obtained from the relevant patients for the use of these figures.

Ethics

Authorship Contributions

Concept: Z.K.C., B.H., Design: Z.K.C., B.H., Data Collection or Processing: Z.K.C., Analysis or Interpretation: Z.K.C., B.H., Literature Search: Z.K.C., Writing: Z.K.C.

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