Editorial

Idiopathic granulomatous mastitis

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Comment on: Ozcan BB, Merchant K, Goldberg J, *et al.* Can imaging findings predict the outcome of idiopathic granulomatous mastitis? Ann Breast Surg 2022;7:35.

Keywords: Granulomatous mastitis; inflammatory breast disease; idiopathic mastitis; granuloma

Received: 28 November 2022; Accepted: 15 December 2022; Published online: 03 February 2023.

doi: 10.21037/abs-22-57

View this article at: https://dx.doi.org/10.21037/abs-22-57

Introduction

In 1972, Kessler and Wolloch first reported a benign mastitis, characterised by non-caseating granulomata and abscess formation, which mimicked appearances typical of inflammatory breast malignancy (1). This clinical entity was subsequently termed idiopathic granulomatous mastitis (IGM), and is a chronic condition characterised by recurrent breast inflammation of unclear aetiology. IGM is rare, with a prevalence estimated at 2.4 per 100,000 women aged between 20 to 40 years (2); racial variation is noted, with increased incidence in women of Hispanic (2) and Asian (3) heritage. Imaging findings in IGM by ultrasonography (US), mammography or magnetic resonance imaging (MRI) are frequently non-specific and have overlapping features with inflammatory carcinoma (4), thus diagnosis usually requires confirmation by tissue biopsy. Depending on disease severity, treatment options vary from observation in mild cases, to recurrent aspiration, limited surgery, or systemic immunosuppression for persistent disease (5). Given the diagnostic and therapeutic challenges posed by IGM, there are many proposed treatment algorithms with no consensus on a 'gold-standard' model of care (5). As disease resolution may take up to 20 months, long-term follow-up of patients is usually required (6). In a new retrospective analysis by Ozcan *et al.* (7), clinical follow-up was found to be non-inferior to imaging in predicting disease outcomes. This novel finding supports a shift away from resource-intensive and potentially unnecessary imaging in the long-term management of IGM patients.

Pathophysiology

The precise aetiology and pathophysiological mechanisms underlying IGM are not yet fully understood (8). It has been previously postulated that IGM emerges after an initial accumulation of glandular proteinaceous secretions, leading to ductal ectasia followed by perforation. This triggers an inflammatory response, leading to the inflammation and granuloma formation characteristic of IGM (8,9). The association of granulomatous mastitis with factors promoting mammary gland secretions, including oral contraceptive use, hyperprolactinemia, pregnancy and breastfeeding (9,10) supports this model.

Various other aetiological triggers for IGM have been described, including breast trauma, alpha-1-antitrypsin deficiency and infection with *Corynebacterium* species (8). An immune-mediated process is implicated, given the established efficacy of immunosuppression in inducing disease remission (11). Autoimmunity may arise secondary to antigen presentation following duct perforation,

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leading to immune system activation (9). In support of this hypothesis, levels of interleukin (IL)-22/23, cytokines commonly implicated in autoimmune diseases, have been shown to be significantly elevated in IGM patients compared with healthy controls (12). Immunohistochemical staining on tissue specimens demonstrates a T-cell predominance with granulomatous inflammation (13). An association between IGM and serological markers of autoimmune disease such as anti-nuclear antibodies (ANA) and rheumatoid factor (RF) has previously been reported (14) but is not always present (15,16). Overall, only a small proportion of IGM patients have concurrent autoimmune disease, and indeed the patients described by Ozcan *et al.* demonstrate a lack of autoimmune comorbidities.

Clinical features

IGM typically presents as a unilateral breast mass (17); involvement of both breasts is rare (18) as reflected in the study by Ozcan *et al.* where only 9 of 181 women experienced bilateral disease. Associated features such as cutaneous erythema and peau d'orange, nipple retraction and axillary lymphadenopathy (17,19) mimic inflammatory breast cancer, which is frequently misdiagnosed, resulting in significant patient anxiety. Systemic features of inflammation such as fever are not usually present (5).

Diagnosis

Diagnosis of IGM can be challenging due to varied clinical and non-specific radiologic features at presentation, which often overlap other disease processes such as infection or cancer. Risk factors including reproductive age, hormonal imbalance or contraceptive treatment and recent history of pregnancy or lactation should be sought on history. Histological evidence of non-caseating multinucleated giant cell granulomata is supportive, however often repeated biopsies may be needed to demonstrate this characteristic feature (9). Given the idiopathic label, infections or systemic diseases associated with granulomatous inflammation, such as rheumatoid arthritis or granulomatosis with polyangiitis amongst others, need to be excluded prior to diagnosis with IGM; readers are referred to the diagnostic approach presented by Nguyen *et al.* (9).

Microbiology

As seen in the present retrospective review (7), antibiotics are frequently prescribed in IGM due to overlapping clinical features with infective mastitis. Microbiological investigations are useful, and should include blood and tissue culture for routine as well as atypical organisms, including mycobacteria and fungi. Serological testing for exposure to syphilis, fungi, and cryptococcal antigen is also recommended. Isolation of *Corynebacterium* species has been reported in 45% of specimens (20) and its detection, although difficult due to its fastidious nature, allows targeted antibiotic therapy that can be of benefit.

Radiology

The most frequently employed radiological investigations in IGM are mammography and US, with MRI occasionally used due to its improved sensitivity (21). The most common finding on mammography is a focal, asymmetrical density; on sonography, a hypoechoic, irregular lesion with tubular extensions is most frequently seen (22). Ultrasound may also reveal well-defined fluid collections, or overlying skin changes such as induration or nipple retraction (21). In the current study (7), the most common US finding was a hypoechoic collection in 101 out of 133 breasts imaged with US (75.9%), with 54 of these 101 (53.5%) breasts also demonstrating associated skin involvement. Out of 93 breasts receiving mammography, the most common finding was focal asymmetry in 48 out of 93 breasts (51.6%); lymph node involvement occurred in 8 of 93 (8.6%) breasts undergoing mammography. Ultimately, these imaging findings are non-specific and overlap with features seen in other breast pathology, thus tissue sampling remains crucial for a definitive diagnosis.

Management

Systemic corticosteroid therapy is considered the standard of care for IGM (23) being both non-invasive and efficacious. Corticosteroids may be combined with surgery, with some studies suggesting a higher success rate with this approach (24,25). Drawbacks arise due to the multiple adverse effects of steroid use, thus prompting the use of steroid-sparing agents such as methotrexate which can be efficacious in controlling IGM (11). Targeted antibiotic therapy can be useful in IGM cases associated with *Corynebacterium* isolation (9,22). Expectant management may also be pursued, particularly for mild cases featuring small or solitary breast lesions as up to 50% of IGM cases resolve spontaneously (23).

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Surgery

Surgical resection of IGM lesions is widely employed, and may be the preferred approach in limited disease or employed as salvage therapy following failure of corticosteroid therapy (24). A wide excision of the lesion is usually performed; ultrasound-guided aspiration is also useful for drainage of collections (23). Surgical risks include disease recurrence, wound infection and aesthetic considerations related to scarring.

Ozcan *et al.*'s study (7) included a total of 133 breasts with IGM; of these, 131 breasts had first line treatment information available, allowing for the efficacy of various treatment modalities to be analysed. Of these, 69 breasts were treated on initial presentation to the emergency department (ED) and most (65 out of 69 breasts) received antibiotics with the remaining 4 breasts (5.8%) receiving steroids in ED. Once all 131 breasts had been referred to a breast clinic and diagnosed with IGM, 56 of 131 breasts (43%) received corticosteroids as first-line treatment, with expectant management the next most common initial approach in 41 breasts (31%); 14 (11%) breasts also received antibiotics and a minority of 7 breasts (5.3%) underwent invasive surgical excision or incision and drainage as first-line treatments. Overall clinical improvement was observed in 91 of 130 breasts (70%) reviewed at breast clinic follow-up, and no difference was seen in disease outcome between patients who underwent active treatment and those undergoing observation only. These findings favour a more conservative approach to IGM management, allowing for bias owing to the retrospective nature of the study, small sample size of the untreated cohort, and the significant number of patients (42/133) who did not receive US follow-up.

Outlook

Disease recurrence in IGM is relatively common despite treatment, with rates varying with treatment modality; published case series have shown an overall recurrence rate of 25% (10). Re-emergence of disease is less frequent in patients treated surgically than those undergoing non-surgical interventions, with recurrence rates estimated at 5.1% *vs.* 22.7% at 3 months respectively (24). Ozcan *et al.* did not report a clear association between US findings at baseline and disease outcome, raising the possibility that radiological features on presentation might not be predictive of disease trajectory. To contrast this, features such as multicentric disease and fistula formation have previously been reported as predictive of IGM recurrence (26). Further prospective studies are therefore required to clarify this point.

There remains a lack of consensus on the approach to monitoring, although 3–6 monthly imaging has been recommended (6). The findings of Ozcan *et al.* suggest that resource-intensive imaging may be unnecessary, as clinical assessment provides equally reliable surveillance information.

Recommendations

IGM is a chronic condition, which can be debilitating and distressing for patients, both at the time of diagnostic evaluation and during protracted or recurrent disease. Imaging with US or mammography is useful, but histological confirmation remains essential for diagnosis and to exclude malignancy. Detection of granulomata necessitates tissue culture and serological investigations to exclude an infective cause, as well as further assessment for systemic conditions associated with granuloma formation. Expectant management with regular clinical assessment is a reasonable first approach for mild disease; options for more severe or persistent disease include corticosteroids, aspiration or surgical excision. A multidisciplinary approach is recommended to guide investigations and management, and collaboration between surgeon, radiologist, immunologist and microbiologist ensures a comprehensive approach to IGM treatment.

The current study presents a review of 133 breasts with confirmed IGM, with an analysis of demographic features, imaging findings and disease outcomes with various treatment modalities. There was no association evident between imaging features at baseline and eventual disease outcome. Moreover, there was no association between imaging findings and clinical assessment at first follow-up and eventual disease outcome, which is reassuring for patients who may not demonstrate early improvement. The findings of Ozcan *et al.* allow for a less formal approach to serial imaging, with clinical assessment demonstrated as non-inferior. Such an approach may well reduce the burden of appointments and imaging assessments for patients, and allow for improved attendance during follow-up for monitoring of treatment response and complications of therapy.

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Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Breast Surgery*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-22-57/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Kessler E, Wolloch Y. Granulomatous mastitis: a lesion clinically simulating carcinoma. Am J Clin Pathol 1972;58:642-6.
2. Idiopathic granulomatous mastitis in Hispanic women – Indiana, 2006-2008. MMWR Morb Mortal Wkly Rep 2009;58:1317-21.
3. Otto TS, Argobi Y, Lerwill MJ, et al. A retrospective study of idiopathic granulomatous mastitis diagnosis and clinical presentation. J Am Acad Dermatol 2022;86:467-9.
4. Grover H, Grover SB, Goyal P, et al. Clinical and imaging features of idiopathic granulomatous mastitis – The diagnostic challenges and a brief review. Clin Imaging 2021;69:126-32.
5. Bede K, Valente SA. Idiopathic granulomatous mastitis. Ann Breast Surg 2020;4:24.
6. Lai EC, Chan WC, Ma TK, et al. The role of conservative treatment in idiopathic granulomatous mastitis. Breast J 2005;11:454-6.
7. Ozcan BB, Merchant K, Goldberg J, et al. Can imaging findings predict the outcome of idiopathic granulomatous mastitis? Ann Breast Surg 2023;7:35.
8. Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. World J Clin Cases 2014;2:852-8.
9. Nguyen MH, Molland JG, Kennedy S, et al. Idiopathic granulomatous mastitis: case series and clinical review. Intern Med J 2021;51:1791-7.
10. Azizi A, Prasath V, Canner J, et al. Idiopathic granulomatous mastitis: Management and predictors of recurrence in 474 patients. Breast J 2020;26:1358-62.
11. Kim J, Tymms KE, Buckingham JM. Methotrexate in the management of granulomatous mastitis. ANZ J Surg 2003;73:247-9.
12. Saydam M, Yilmaz KB, Sahin M, et al. New Findings on Autoimmune Etiology of Idiopathic Granulomatous Mastitis: Serum IL-17, IL-22 and IL-23 Levels of Patients. J Invest Surg 2021;34:993-7.
13. Erhan Y, Veral A, Kara E, et al. A clinicopathologic study of a rare clinical entity mimicking breast carcinoma: idiopathic granulomatous mastitis. Breast 2000;9:52-6.
14. Ozel L, Unal A, Unal E, et al. Granulomatous mastitis: is it an autoimmune disease? Diagnostic and therapeutic dilemmas. Surg Today 2012;42:729-33.
15. Altintoprak F, Karakece E, Kivilcim T, et al. Idiopathic granulomatous mastitis: an autoimmune disease? ScientificWorldJournal 2013;2013:148727.
16. Asoglu O, Ozmen V, Karanlik H, et al. Feasibility of surgical management in patients with granulomatous mastitis. Breast J 2005;11:108-14.
17. Baslaim MM, Khayat HA, Al-Amoudi SA. Idiopathic granulomatous mastitis: a heterogeneous disease with variable clinical presentation. World J Surg 2007;31:1677-81.
18. Velidedeoglu M, Kilic F, Mete B, et al. Bilateral idiopathic granulomatous mastitis. Asian J Surg 2016;39:12-20.
19. Steuer AB, Stern MJ, Cobos G, et al. Clinical Characteristics and Medical Management of Idiopathic Granulomatous Mastitis. JAMA Dermatol 2020;156:460-4.
20. Taylor GB, Paviour SD, Musaad S, et al. A clinicopathological review of 34 cases of inflammatory breast disease showing an association between orynebacterial infection and granulomatous mastitis. Pathology 2003;35:109-19.

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21. Sripathi S, Ayachit A, Bala A, et al. Idiopathic granulomatous mastitis: a diagnostic dilemma for the breast radiologist. Insights Imaging 2016;7:523-9.
22. Hovanessian Larsen LJ, Peyvandi B, Klipfel N, et al. Granulomatous lobular mastitis: imaging, diagnosis, and treatment. AJR Am J Roentgenol 2009;193:574-81.
23. Yuan QQ, Xiao SY, Farouk O, et al. Management of granulomatous lobular mastitis: an international multidisciplinary consensus (2021 edition). Mil Med Res 2022;9:20.
24. Wang J, Zhang Y, Lu X, et al. Idiopathic Granulomatous Mastitis with Skin Rupture: A Retrospective Cohort Study of 200 Patients Who Underwent Surgical and Nonsurgical Treatment. J Invest Surg 2021;34:810-5.
25. Godazandeh G, Shojaee L, Alizadeh-Navaei R, et al. Corticosteroids in idiopathic granulomatous mastitis: a systematic review and meta-analysis. Surg Today 2021;51:1897-905.
26. Basim P, Argun D, Argun F. Risk Factors for Idiopathic Granulomatous Mastitis Recurrence after Patient-Tailored Treatment: Do We Need an Escalating Treatment Algorithm? Breast Care 2022;17:172-9.

doi: 10.21037/abs-22-57
Cite this article as: Xu G, Limaye S. Idiopathic granulomatous mastitis. Ann Breast Surg 2023;7:31.

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