Annals of Medicine and Surgery 70 (2021) 102792

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Review

Assertive clinical practice in managing patients with idiopathic granulomatous mastitis: Review of literature

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ARTICLE INFO

Keywords:
Assertive
Clinical practice
Managing
Patients
Idiopathic granulomatous mastiti

ABSTRACT

Idiopathic granulomatous mastitis (IGM) is a benign persistent inflammatory breast entity characterized histologically by lobulo centric granulomas. Diagnosis may be difficult and involves a strong index of suspicion. There are plentiful studies are published which render the disease more frequently than expected. The strategy for imaging IGM depends on patient age, clinical manifestations, and risk factors. Patients have an excellent prognosis when they are appropriately treated. The management remains contentious, good judgment is required to ensure optimum treatment form and timing.

1. Introduction

Idiopathic granulomatous mastitis (IGM) is a rare chronic benign inflammatory breast condition that was first described in 1972 [1]. IGM is distinguished histologically by non-caseating granulomas with a lobulo-centric pattern that is often correlated with the development of micro-abscesses, with variable clinical presentations [2,3], and the diagnosis is made by exclusion causes of mastitis.

The etiology of IGM is hypothetical [4]. Therefore, the diagnosis and treatment represent a challenge.

The purpose of this article is to review the etiology, clinical presentation, differential diagnosis of IGM and of breast imaging, as well as valuable resources to promote a better clinical practice to manage IGM.

2. Literature search

A PubMed search was used to identify all articles regarding GM. A total of 612 articles from the time frame of 1972–2021 were identified utilizing the search term of ((Granulomatous Mastitis) OR (Granulomatous Lobular Mastitis)) OR (idiopathic Granulomatous Mastitis). Language is limited to "English". There were only 4 review articles and meta-analysis and systemic review [39,54,55,61], the rest was based on anecdotal data as case reports and case series. We modify our topic during the research process. We check for specific guidelines concerning the number of sources we are required to use, the kinds of sources are we able to use - books vs. web sites vs. journal articles, the type of research we are you being asked to conduct. As a review of what research has been done? the length of our final project, the depth of our project as an overview of the subject, the scope we are required to cover as a report of current developments.

This study was planned in advance to achieve our objectives in this overview which were; screening titles and abstracts, full texts, data extraction and export, import citations, upload references about the assertive clinical practice in managing patients with idiopathic granulomatous mastitis. Our Overview is a relatively new approach to synthesizing evidence, and research methods and associated guidance about managing Patients with Idiopathic Granulomatous Mastitis. Within this paper we aim to help readers understand key issues which are essential to consider when managing this condition. These issues relate to the development of clear, relevant perspective.

3. Epidemiology

It affects young women between 17 and 42 years of age within the reproductive and post-childbearing period [2,3,and4]] patients. However. Cases between 11 and 83 years of age were reported. The mean age at presentation was 36.5 years [22] 5–10% could happen during pregnancy [14,16,18,19] The majority of patients report a nursing history, at most it happens 6 months to 2 years after the cessation of breastfeeding [6]. There are racial factors that predispose to the development of IGM [19] more in non-Caucasian, where Asia and Middle-East have suggested a possible higher prevalence [21] than woman of Hispanic origin.

4. Pathophysiology

There are ample theories around granulomatous mastitis.

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https://doi.org/10.1016/j.amsu.2021.102792
Received 23 June 2021; Received in revised form 24 August 2021; Accepted 2 September 2021
Available online 11 September 2021

Nevertheless, non-have been proven or yet fully understood, and they are based on anecdotal observations. Several precipitating factors have been proposed; it includes pregnancy, lactation, hyperprolactinemia, α1-antitrypsin deficiency, oral contraceptive use, trauma, diabetes, autoimmune disease, and smoking. Hyperprolactinemia and smoking and are the only factors with well-established associations with GM [5,6]. Several mechanisms were proposed, non-yet is proven. The theories are centered on 3 mechanisms:

4.1. Autoimmune

where an insult such as trauma, infection, or chemical irritation, triggers a local immune response to the ductal epithelial cells in the breast, that allows luminal secretions to escape toward the lobular connective tissue. These changes IL [7,24,25,27,28]. As reported by Saydam et al. the significant differences in IL-22 and −23 levels between GM patients and the control group were thought to contribute to autoimmunity in GM pathogenesis [28] in addition, it is been reported that rheumatoid factor (RF), ANA, and anti-dsDNA antibodies were positive in all patients with GM without other clinical manifestations suggestive of autoimmune [31,34].

4.2. Hormonal

Given that GM is usually detected in women in childbearing age and a history of parity these factors have supported the hormonal role [3]. Hyperprolactinemia has also been considered responsible as it could be identified in up to 30% of patients [43]. In addition, the occurrence of GM without a history of recent pregnancy is uncommon [6].

4.3. Infection

although no micro-organism has been consistently isolated from GM, there is a consistent presence of the Gram-positive bacillus Corynebacteria. Especially C. kroppenstedtii [7,10,11,23,35] with the histological findings of cystic neutrophilic granulomatous mastitis (CNGM) [53].

5. Clinical presentation

The most common symptoms of granulomatous mastitis are breast lumps 48–100%and mastalgia. Abscess formation happen in 16–52% of cases on presentation [23]. External draining sinuses, erythema and edema also reported [38].The nipple is rarely involved, although nipple retraction and ulceration and discharge have been documented (4). Patients may also have more bizarre presentations, particularly in subclinical forms [5,13] Nevertheless, systemic symptoms such as fever are generally not present [43].Although very rare, it can also be seen in male patients [37,40].

Usually GM affect peripheral breast tissue in 50% of time, sub areolar 25%, and diffuse GM lesions 25%, of time [7,9].only 15% of patients may present with regional lymphadenopathy [2], fortunately the disease is unilateral however it can be seen in both breasts in 25% of cases [37,47].

6. Differential diagnosis

The differential diagnosis of "granulomatous mastitis" is broad and is made by exclusion of other possible causes, such as infections (tuberculosis,histoplasmosis and actinomycosis), periductal mastitis (periductal fibrosis),autoimmune disorders (sarcoidosis and Wegener's granulomatosis), part of systemic disease (Diabetic Fibrous Mastopathy) foreign body reaction and fat necrosis [43,47,52].

6.1. Inflammatory breast cancer

Invasive carcinoma is the most important entity to consider in the differential diagnosis when assessing any breast abnormality.

6.2. Infective mastitis

Infective mastitis is the most common diagnosis to exclude in the setting of suspected GM in women of childbearing age. To add to the dilemma infective mastitis may present with a superimposed abscess. To differentiate infective mastitis from GM cultures revealing common skin bacteria,in up to 40% of breast abscesses, such as S aureus, Staphylococcus albus, or Streptococcus species should be rolled out [62,64]. Atypical causes of infective mastitis, e.g. Mycobacterium, Echinococcus, Actinomyces, and resistant bacterial strains, also should be considered in patients who have infections that are nonresponsive to empirical antibiotic therapy. By definition, granulomatous mastitis should yield negative cultures, although an association with Corynebacterium infection has been proposed, with cystic neutrophil granulomatous mastitis [10].

6.3. Periductal mastitis

It closely resembles granulomatous mastitis in clinical manifestations and imaging examination, in contrary to GM, patients with periductal mastitis present with nipple involvement such as discharge and retraction. Histologically periductal mastitis have more foam cell and deciduous ductal epithelial cells exist commonly around the ducts and lobules, it may have giant cells but usually lacks formed granulomas [6,51]

6.4. Vasculitis

Patients with connective tissue disease demonstrate less than 1% of breast involvement. Most patients will have a positive anti-neutrophil cytoplasmic autoantibody (ANCA) and rheumatoid factor (RA). Serological studies include *p*-ANCA, c-ANCA, and the recently introduced PR-3 ANCA ELISA are helpful diagnostic features to differentiate GM from vasculitis [68,69].

6.5. IgG4-related sclerosing mastitis

The concept of immunoglobulin (Ig) G4-related sclerosing disease was proposed in Japan to explain similar pathological imaging findings and responses to steroid therapy. Breast is one of the extra-pancreatic lesions [58]. It present as painless breast masses with histologically featuring dense lymphoplasmacytic infiltrate with extensive sclerosis, large numbers of IgG4+ plasma cells, and elevated serum IgG4 concentration [10].

7. Diagnosis

7.1. Imaging

The role of imaging in the evaluation of biopsy-confirmed GM is to enable the clinician to the size of lesions, identify abscess formation and the possibility of intervention, and evaluate the interval change in lesions after treatment response [6].

7.1.1. Ultrasonography

It is the first modality used in all age groups Lesion appears irregular hypoechoic lesion with tubular extension is the most frequent finding. Isolated ill-defined hypoechoic or heterogeneous lesion as the second most common finding [43]. At greyscale, granulomatous mastitis lesions are seen as very heterogeneous lesions with a wide range of brightness [5] (Fig. 2).

In advanced cases, the disease may present as fluid collections or abscess cavities. Ultrasound is useful for the documentation of sinus tracts extending to the skin surface, also helpful in the evaluation of

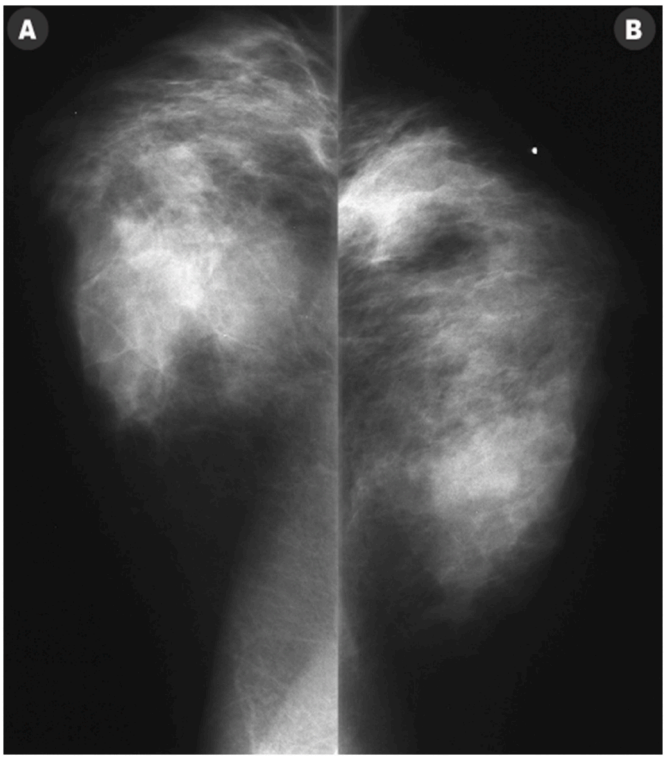

Fig. 1. Mamography showed Granulomatous Mastitis.

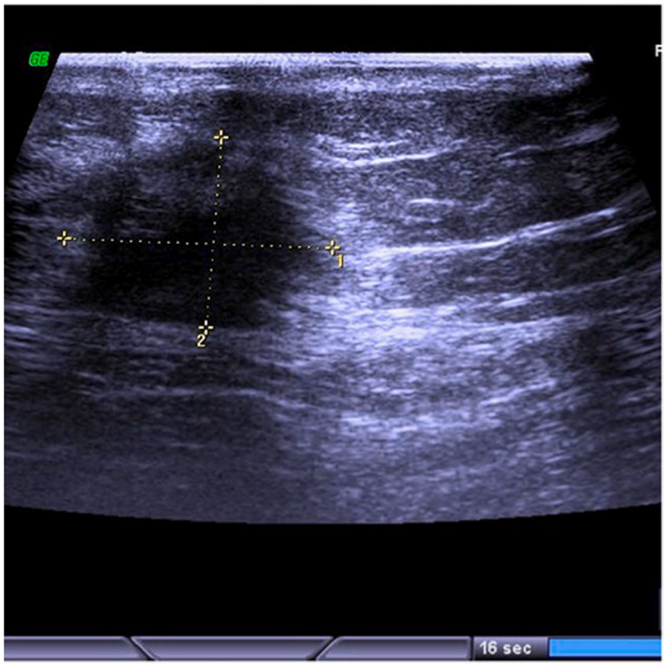

Fig. 2. Ultrasonography of the breast showed granulomatous mastitis.

enlarged axillary lymph nodes, which demonstrate reactive features [8]. Additionally, it is the main follow-up tool after an appropriate treatment regimen (70) (Figs. 5–9).

7.1.2. Doppler ultrasonography

75% of patients had increased arterial and venous vascularization within and around the breast lesion [44]. Prominent arterial and venous Doppler signals can be found in the inflamed parenchyma [11]. In addition, Doppler signals are also helpful for biopsy guidance. if granulomatous mastitis is suspected, biopsy specimens must be obtained from vascularized areas to achieve an appropriate histologic diagnosis [7].

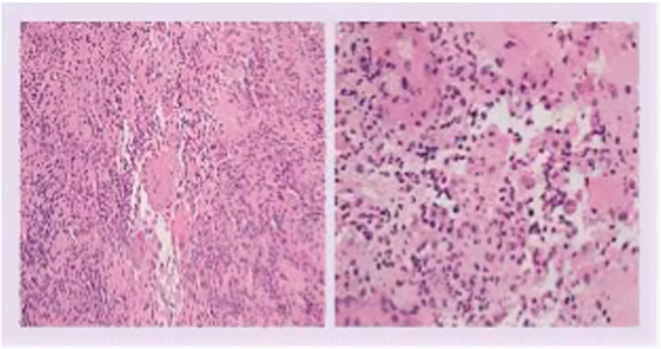

Fig. 3. Histopathology of granulomatous mastitis.

7.1.3. Elastography

Compressive elastography in granulomatous mastitis shows soft properties with low elasticity scores and strain ratios and internal velocities compared to malignant lesions [5,50].

7.2. Mammography

It is used for ladies 40 years old or more. Findings of GM are non-specific, focal asymmetric density is the most frequent finding. Less common mammographic findings included an irregular mass, Global asymmetry, regional asymmetry, trabecular thickening or multifocal involvement may also be noted in the affected breast [7,9]. Skin thickening and nipple retraction were seen with subareolar involvement. .GM is not usually associated with calcifications [12]. In many cases, the affected breast may appear larger than the contralateral breast, a finding most apparent on a mediolateral oblique view [8].

Although it may not show any findings particularly in dense breasts [5,6]. often, the mammographic appearance of GM can be indistinguishable from inflammatory breast cancer prompting further imaging evaluation (Fig. 1).

7.2.1. Magnetic resonance imaging

MRI may play a complementary role to increase the conspicuity of lesions that are not visualized by mammograms and ultrasound adequately due to parenchymal edema, to exclude a diagnosis of inflammatory breast cancer [5]. The radiologic findings of GM have a wide spectrum on MRI. Although no radiographic findings are specific for GM, non-mass-like enhancing lesions were more frequent than mass-like lesions [57]. Time-signal intensity curve analyses can provide useful information in distinguishing GM from malignant breast lesions yet, it is not definitive [46,56].

Edematous inflammation features in the peripheral parenchyma were common findings [45]. Associated features on MRI, including skin thickening, skin retraction, and nipple retraction have also been described [8,46,49] (Figs. 10 and 11).

7.3. Histopathology

Histopathological evaluation is the gold standard It is characterized by the presence of epithelioid non-caseating granulomas with epithelioid histiocytes in a predominantly neutrophilic and eosinophil background, limited to the mammary lobules [13,48], with occasional features of fat necrosis, abscesses and sinus tract. Extensive inflammation may obliterate lobulocentric character. Ductal and periductal inflammation usually minor [63].

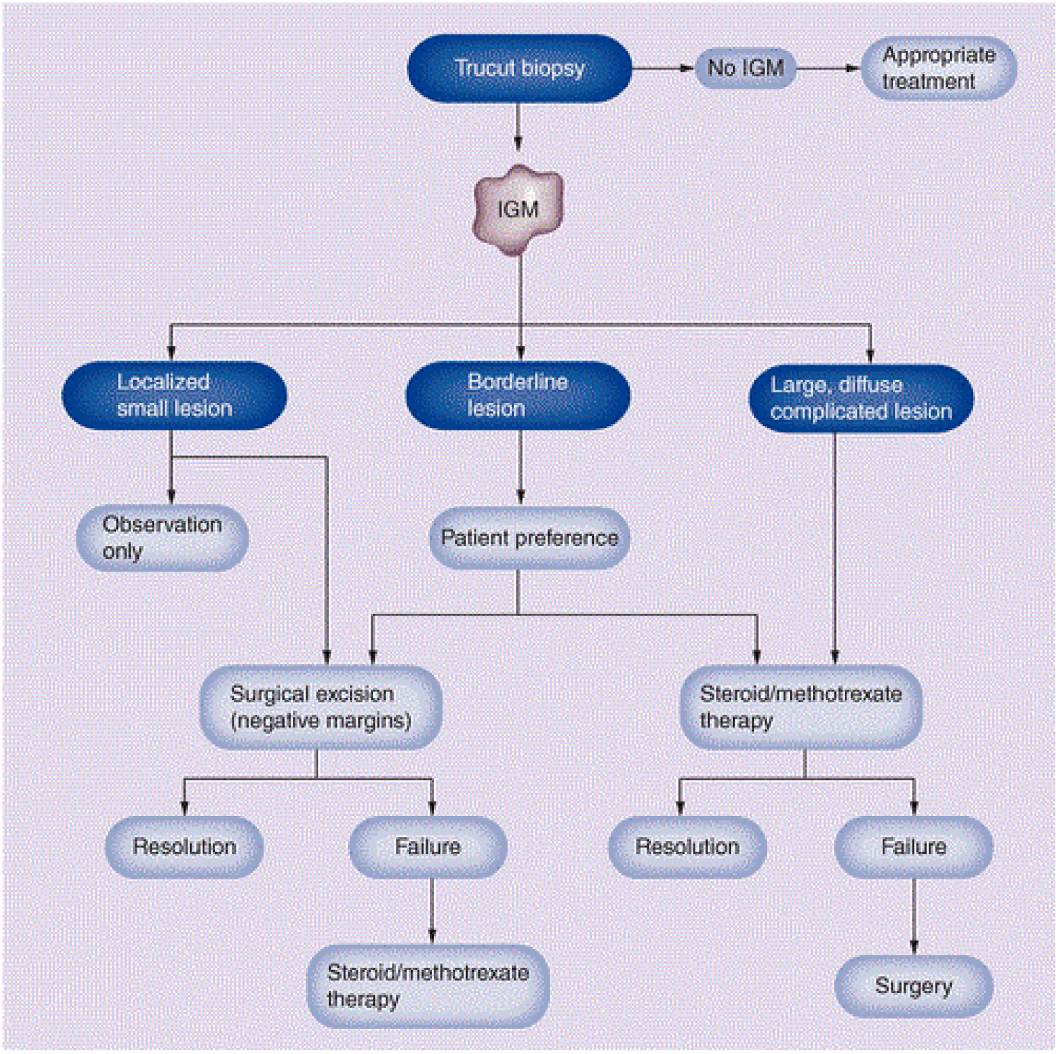

Fig. 4. Management of granulomatous mastitis.

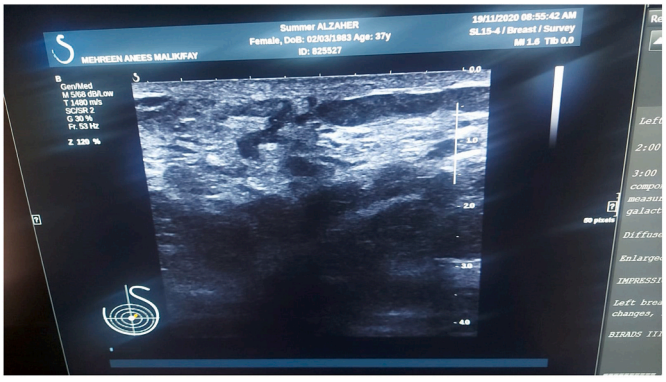

Fig. 5. Ultrasonography of the breast showed granulomatous mastitis.

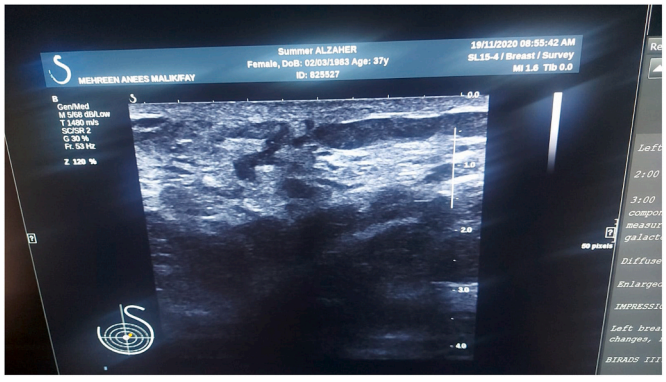

Fig. 6. Ultrasonography of the breast showed granulomatous mastitis.

Necrosis is rare, a finding typically seen with tuberculous mastitis An associated inflammatory infiltrate composed of multi-nucleated giant cells, plasma cells and lymphocytes are typically isolated within affected lobules Depending upon severity, this inflammatory response may extend into adjacent breast lobules. Involved parenchyma demonstrates loss of acinar structure and damaged ducts. Formation of sterile micro abscesses may also be demonstrated [8]. A large specimen is necessary to detect specific changes implying the localization of inflammation [1].

Deferential diagnosis showed in Table 1 and Fig. 3.

8. Management

Treatments may be tailored to the nature of the signs, the extent of the lesions, and the general condition of the patient. Many treatment algorithms can be found in the literature, but none have gained widespread acceptance.

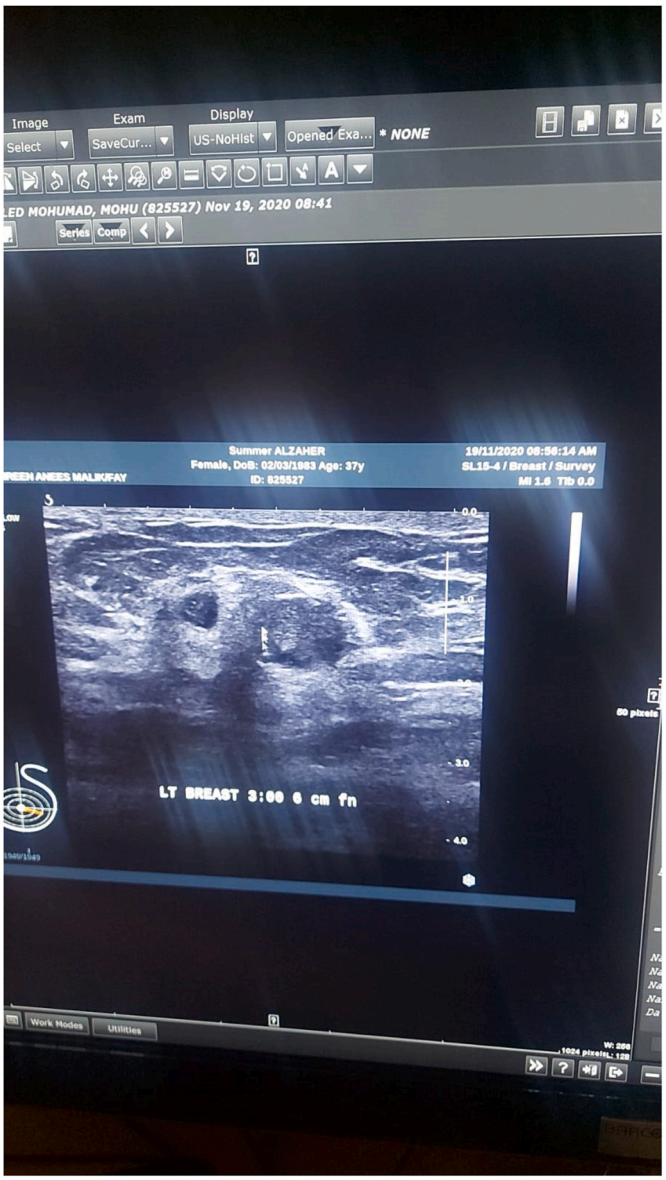

Fig. 7. Ultrasonography of the breast showed granulomatous mastitis.

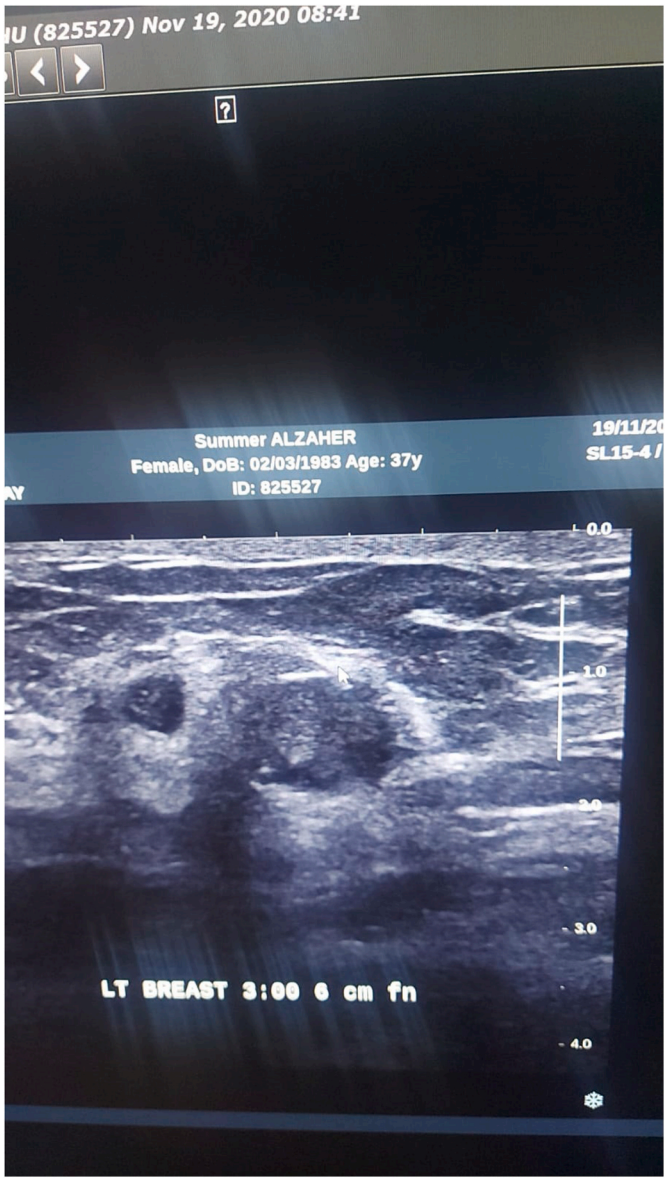

Fig. 8. Ultrasonography of the breast showed granulomatous mastitis.

8.1. Surveillance and observation

As the natural history of GM is supposed to be self-limiting, close surveillance was proposed as a treatment option [1]. Patients present with a range of symptoms and abscess sizes, but if the symptoms are mild to painless along with small lesions, mildly tender palpable mass, observation should be the treatment of choice. It can avoid the complications of repeated surgical excisions and steroid therapy. Complete resolution was reported up to 50% [16] There is reported a spontaneous remission of GM lesions in symptomatic patients after 5–24 months [26], irrespective of the treatment administered. Close regular follow-up every 2–3 months [29],

There is currently no consensus regarding the radiologic surveillance of GM; however, some authors have endorsed a protocol involving mammography performed annually and ultrasound performed every 3–6 months after the acute episode until the disappearance of symptoms [17].

8.2. Medication therapy

8.2.1. Antibiotics and pain management

Given the far more common incidence of infective mastitis and the overlapping most patients who are treated with empirical antibiotic therapy targeting common pathogens such as Staphylococcus (including methicillin-resistant variants) and Streptococcus. Using cloxacillin, cephalexin, or clindamycin) [33]. If GM diagnosis was established especially cystic neutrophilic type, then lipophilic antibiotics, such as doxycycline, clarithromycin and rifampicin have been recommended as 70% resistance rate to penicillin in GM patients with Corynebacterium [53] For symptomatic pain relief, nonsteroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice to help with the inflammatory pain that corresponds to the GM masses [3].

8.2.2. Bromocriptine

Several cases reports have shown to be most effective in cases of GM with concomitant hyperprolactinemic states [9]. if prolactin levels are elevated, anti-prolactin therapy can be considered alone or in combination with steroids [59,60].

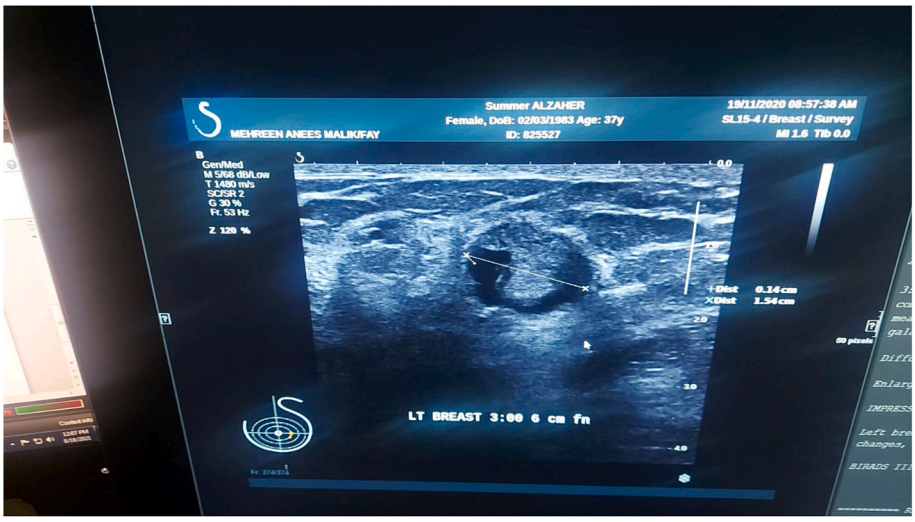

Fig. 9. Ultrasonography of the breast showed granulomatous mastitis.

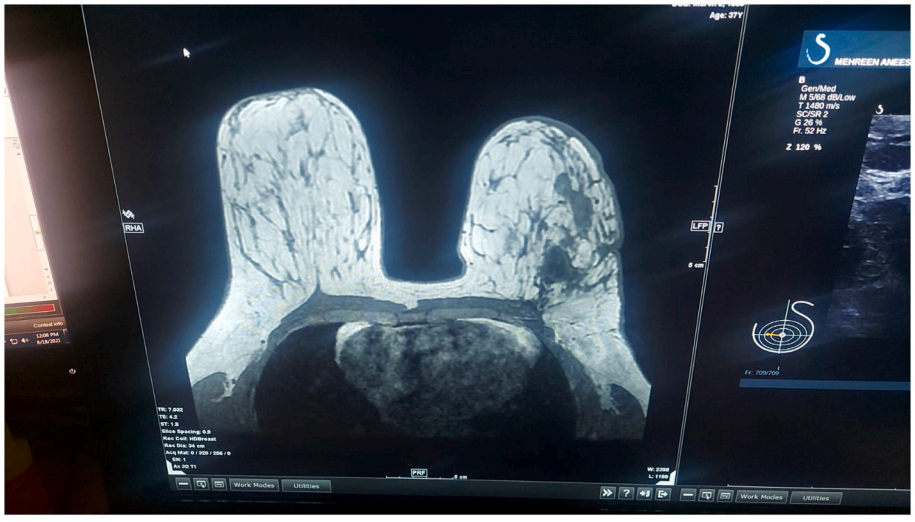

Fig. 10. Showed magnetic resonance imaging of granulomatous mastitis.

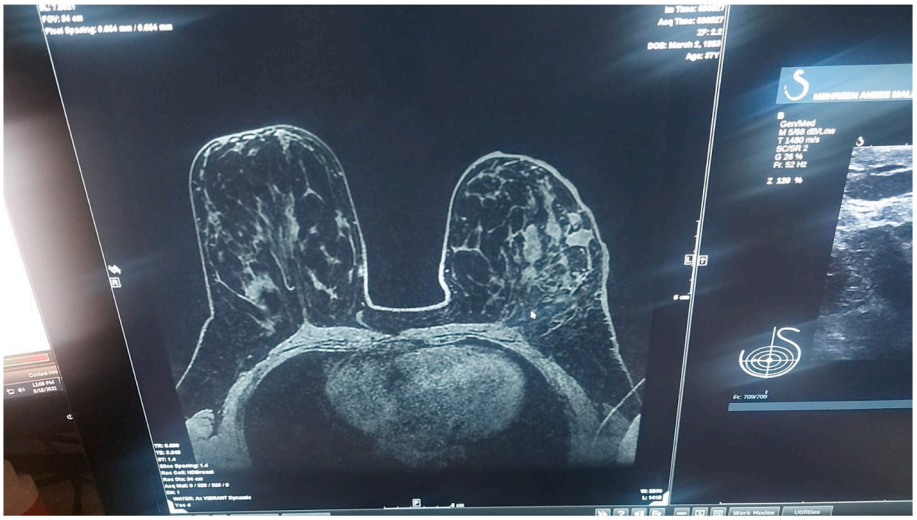

Fig. 11. Showed magnetic resonance imaging of granulomatous mastitis.

Table 1
Deferential diagnosis of granulomatous mastitis.

Granulomatous Lobular Mastitis	Sarcoidosis
Centered on lobules	Widespread distribution
Granulomas may not be well formed	Well-formed tight granulomas
Associated inflammation may be extensive	Frequently lacks extensive accompanying inflammation (naked granulomas)
May have associated fat necrosis and abscess	Necrosis and abscess rare
Granulomatous Lobular Mastitis	Mammary Duct Ectasia
Centered on lobules	Centered on ducts
Granulomatous inflammation	May have giant cells but usually lacks formed granulomas
Nearly all cases postpartum	May occur without associated pregnancy
Granulomatous Lobular Mastitis	Puerperal Mastitis
No infectious organisms	Bacterial infection
Mean interval two years from delivery	Recent delivery

8.2.3. Steroids

The utilization of steroids for GM is the first-line treatment for many studies [30,36,46,56,and66]] If the prediction of the efficacy of corticosteroid therapy is possible, early recognition and administration of corticosteroid treatment might prevent invasive surgical treatment that deforms the breast. In addition, it should be used as first line for patients with concerns about surgical scarring, oral steroids [39].

Oral steroids are commonly used and have documented success rates up to 72–80%. Complete remission is reported from 5 to 10 months [46]. Weight gain, hyperglycemia, myopathy, oral candidiasis, and gastritis were reported as side effects of corticosteroid treatment. These side effects are not critical but ameliorable, Satisfactory results have been reported with combined therapy consisting of surgery following steroid therapy was used with wide excisions with total histological regression [42,65].

Topical steroids were proposed as an alternative to oral steroids due to having less systemic side effects,recurrence rates for topical steroid use range from 10 to 18% [66]. Topical plus systemic steroids were examined and topical steroids had the best results with the lowest recurrence rate of 14.7% [36,67].

Steroid injections directly into the GM lesions are the newest advancements, it more successful in a small area with no fistula formation [35].

8.2.4. Immune modulators

Methotrexate (MTX), an immunosuppressive agent, has also been successful in the treatment of IGM. It is particularly useful in cases of steroid-resistant GM and in patients who develop steroid-associated complications [14]. The pharmacological dosing for MTX is 10–15 mg/week and increasing to 20–25 mg/week given either orally or subcutaneously based on clinical response with the help of rheumatologist [41]. Reported adverse effects range from elevated liver enzymes and hair loss to more mild symptoms such as nausea, decreased appetite, and mild headaches [14].

Azathioprine is another immunosuppressant that can be used alternatively in patients who develop methotrexate-induced pneumonitis [32] hydroxychloroquine, mycophenolate mofetil (CellCept) and colchicine may, however, be attractive alternatives [13,31,41].

8.3. Surgical treatment

The utilization of surgical intervention as first-line therapy has reduced. Excisional surgery showed the best results as regard healing time [30]. There is a trend now toward more minimally invasive surgical intervention such as aspiration for abscesses. Surgical methods vary from wide surgical excision, and mastectomy [11,20].

Unfortunately, surgical management had a high remission rate with a relatively low recurrence rate, with or without steroids. Thus, surgery was a suitable option for patients requiring rapid remission [39]. Although the literature has demonstrated that wide surgical excision has been successful, but it carries high recurrence rates,even with mastectomy, range up to 50%, complications quite devastating such as extensive scarring, as well as delays in both would healing and fistula formation [1,15].

Wide local excision requires a free margin ranging from 5 to 10 mm which might be impractical, impractical [15]. Thus large inflammatory masses encompassing 50% of the breast in whom medication treatment was unsuccessful, surgery may be the best option [7], The role of I&D is controversial because it may not improve the condition and may lead to intractable incision tracks, which subsequently lead to sinus formation (Fig. 4).

9. Conclusion

Idiopathic granulomatous mastitis (IGM) is common in younger women of childbearing age and may be clinically, radiologically, and cytologically similar to breast carcinoma. Definitive diagnosis must be rendered histologically, which is largely being accomplished with percutaneous tissue needle biopsy techniques, but can necessitate open biopsy. IGM must be distinguished from infectious and known autoimmune disorders of the breast. When malignancy is established histologically, breast cancer is treated in a multidisciplinary environment. In the context of a multidisciplinary breast cancer conference, IGM is unlikely to be misdiagnosed as carcinoma. IGM may be treated by either surgical excision or conventional therapies, either as an initial or sequential procedure. The specific care plan can be informed by the nature of the lesion and related cutaneous signs, as well as the nature of the symptoms. Milder types of IGM can resolve spontaneously without any formal therapeutic intervention, but disease progression should be closely monitored.

10. Provenance and peer review

Not commissioned, externally peer reviewed.

Annals of medicine and surgery

The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

No conflicts of interest.

Please state any sources of funding for your research

All sources of funding should be declared as an acknowledgement at the end of the text. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

No funding sources.

Ethical approval

Research studies involving patients require ethical approval. Please state whether approval has been given, name the relevant ethics committee and the state the reference number for their judgement.

IRB-KKUH-KSUMC- 982709092.

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions.

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written and signed consent obtained.

Author contribution

Please specify the contribution of each author to the paper, e.g. study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways should be listed as contributors. Nuha Alsaleh performed; study concept, design, data collection, data analysis, interpretation and wrote the paper.

Registration of research studies

In accordance with the Declaration of Helsinki 2013, all research involving human participants has to be registered in a publicly accessible database. Please enter the name of the registry and the unique identifying number (UIN) of your study.

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1. Name of the registry:

   N/A.

2. Unique Identifying number or registration ID:

   N/A.

3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

   N/A.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

King Saud University Medical City.

Declaration of competing interest

None.

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