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Idiopathic granulomatous mastitis – A diagnostic and therapeutic challenge: Report of three cases and literature review

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Abstract: *Idiopathic granulomatous mastitis (IGM) also referred to as nonpuerperal mastitis or granulomatous lobular mastitis, is a rare, benign, chronic, inflammatory disorder of the breast. Up to date, the exact aetiopathogenesis of IGM remains poorly understood. Patients typically present with painful breast mass, inflammation symptoms, abscess and fistula which can be confused with inflammatory breast cancer. IGM mimics breast malignancy not only clinically but also radiologically, the anatomopathological examination remains then the gold standard for positive and differential diagnosis. On the microscopic level, IGM presents as non-caseating granulomas and micro-abscess formation centred on the breast lobules. IGM is not only a diagnostic challenge, but also a therapeutic one since treatment is only symptomatic and not consensual. However, recent evidence suggests a superiority of medical treatment over surgical resections which are correlated to poor wound healing, high risk of recurrence and poor aesthetic outcomes. Oral, intra-lesional or topical corticosteroid therapy remains the first-line option for treating IGM. The aim of this paper is to remind clinicians of this entity which may imitate breast malignancy but remains a differential diagnosis, to review the current literature and take stock of the latest diagnostic and therapeutic progress in the subject and to contribute to the literature by reporting our cases.*

Keywords: idiopathic granulomatous mastitis, rare breast disorders, breast malignancy, anatomopathological examination, steroids, surgical resection

Introduction

Idiopathic granulomatous mastitis (IGM) also referred to as nonpuerperal mastitis or granulomatous lobular mastitis, is a form of benign chronic breast inflammation [1]. Historically, it was in 1972 when *Kessler* and *Wolloch* first reported this disease, then further details were given in a five-case series by *Cohen* in 1977 [1]. Epidemiologically, IGM is a rare entity, representing only 0.44 to 1.6% of breast biopsy samples according to an Indian study conducted in 2020 [2]. This rarity makes this disorder a diagnostic and therapeutic challenge.

Cases presentation

First case:
We report the case of Mrs T.O., aged 35 at presentation, multiparous and breastfeeding, who was admitted to our centre for management of left mastodynia associated with skin changes evolving for 6 months. The breast examination revealed B cup breasts, with skin induration, nipple retraction and fistula (figure 1). Palpation was difficult due to the pain and no mass was found. Ultrasound examination has objectified multiple heterogeneous - hypoechoic masses with indistinct margins distributed throughout the breast, with posterior acoustic shadowing and multiple abscesses. An ultrasound-guided micro-biopsies was performed with anatomopathological and immunohistochemical (IHC) examinations of the samples. The non-caseating granulomas centred on lobules were consistent with Idiopathic granulomatous mastitis.

The patient benefited from high dose prednisolone therapy with progressive reduction (80 mg daily for one week, with weekly reductions of 10 mg per day, over a total treatment period of 8 weeks) combined with antibiotic therapy based on amoxicillin - clavulanic acid. Complete clinical and radiological regression was observed within 12 months without recurrence at three years follow-up.

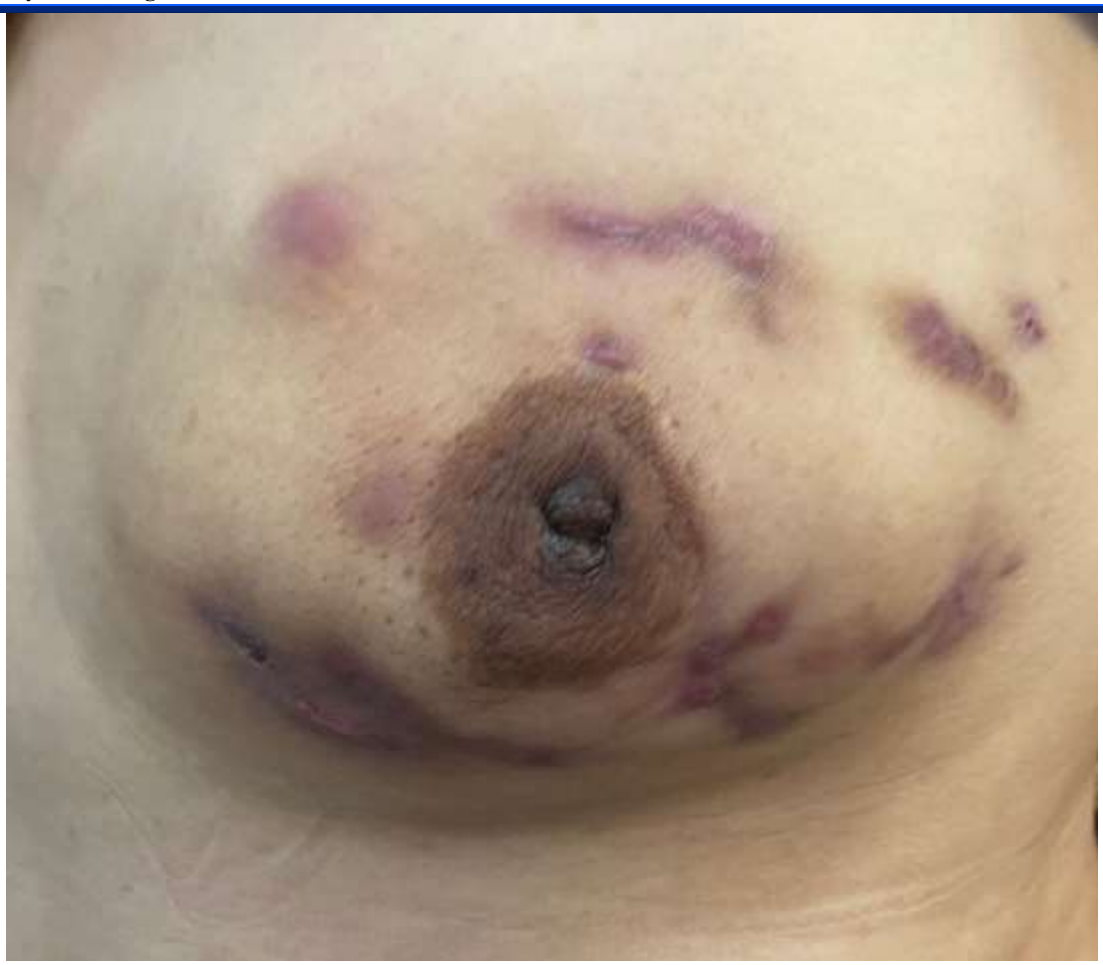


Figure 1: Skin changes within our first patient (Induration, nipple retraction and fistula)

Second and third cases:

The second and third cases (Mrs D.R. and Mrs B.Z.) were aged 49 and 51 at presentation respectively, both were multiparous with breastfeeding history, they were consulted for management of breast masses discovered on auto-palpation and evolving for 1 and 3 months respectively. The breast examination revealed B and C cup breasts respectively, with nodules in the inferolateral (ILQ) and superolateral (SLQ) quadrants respectively, classified clinically as cT2N0Mx and radiologically as ACR4a. Ultrasound-guided micro-biopsies with an anatomopathological and IHC study was performed revealing non-caseating granulomas that are consistent with Idiopathic granulomatous mastitis (figure 2). The same previous therapeutic protocol was proposed to both patients, with a favourable outcome within 6 months without recurrences at three- and two-years follow-up respectively.

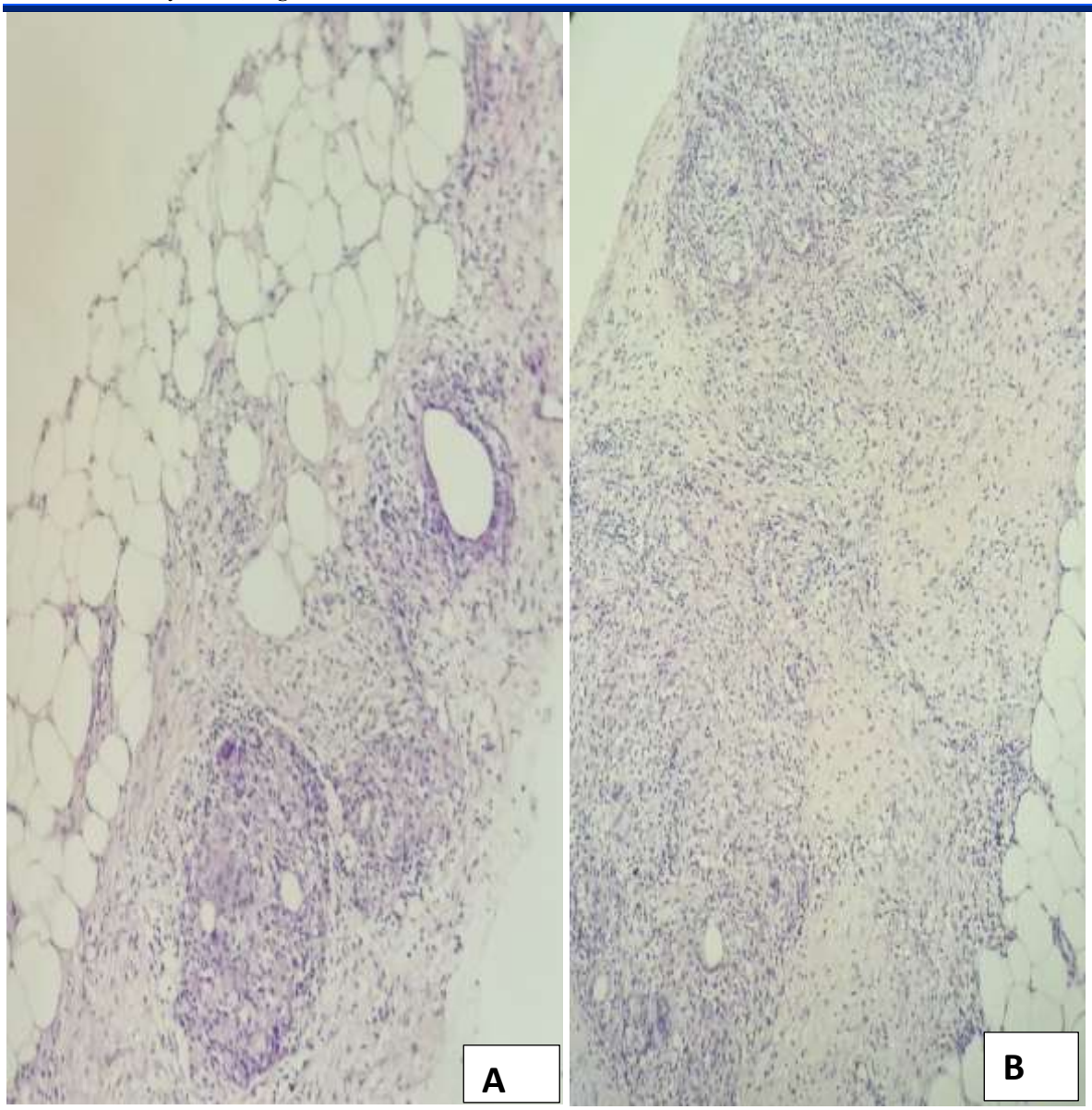


Figure 2: Histologic features of IGM. A: non-caseating granulomas. B: Inflammatory cells infiltrating the breast stroma.

Discussion

Idiopathic granulomatous mastitis (IGM) can be observed at any age with the mean age at diagnosis ranging from 32 to 35 years [1]. In our series, IGM was observed in older patients (35, 49 and 51 years). Some authors have also reported cases of this disease occurring in men [1]. Certain studies have concluded that Spanish, Asian and Middle Eastern ethnicities are more exposed to this breast disorder [1].

To date, the etiopathogenesis of IGM is not fully understood and several hypotheses have been put forward to explain the onset of the disease.

IGM can be considered as an autoimmune disease. Immunomodulators such as steroids and methotrexate have proven their effectiveness in treating IGM. Moreover, autoimmune antibodies (like rheumatoid factor and anti-nuclear antibody) have been positively expressed in some IGM patients. Recent research has shown also a significantly elevated serum levels of interleukin 17, 22 and 23 in these patients.

Furthermore, IGM has been accompanying some autoimmune manifestations as erythema nodosum. All the aforementioned data support the autoimmune theory regarding the development of IGM [3].

The initiating process of IGM may include milk stasis. Indeed, the process starts with a hormonal imbalance (oestrogen-to-progesterone ratios or hyperprolactinemia) which results in intra-ductal stasis of milk secreted by alveolar epithelial cells of a breast lobule. Milk protein may trigger an autoimmune process and damage the epithelial lining of the duct, which leads to the extravasation of secretions from the lumen of the duct into the adjoining lobular connective tissue. A local inflammatory response develops in response to this ductal efflux. This thesis explains the strong correlation between IGM, pregnancy, and breastfeeding. The rare cases of IGM in nulliparous women are associated with elevated prolactin levels, either due to medications or pituitary tumours [1].
Studies have shown that gram positive bacteria, dominated by *Corynebacterium Kroppenstedtii*, may engage in the regulation of IGM progression [3].
Several other factors were linked to the onset of IGM, including alpha-1 antitrypsin deficiency, diabetes, oral contraceptive use, smoking and trauma [1].
It is important to highlight that IGM don't seem to expose to an increased risk of developing breast cancer.

IGM tends to develop over weeks to months and often clinically mimics malignancy [1]. The consultation delay for our patients ranged from 1 to 6 months. Typically, as in our patients, lesions are unilateral, yet some rare cases of bilateral involvement were reported [1]. The lesions may occur in any quadrant of the breast, with the upper outer quadrant being the most affected and the subareolar region being the least affected [1, 3]. One patient out of our three ones presented a mass occurring in the upper outer quadrant. IGM presents as one or more masses with soft texture and obscure borders. Skin changes such as erythema, oedema, induration, orange peel-like aspect, ulceration and nipple retraction, may be associated, which leads sometimes to confusion with inflammatory breast cancer.

Nipple discharge has also been documented. Abscess often occur in severe or chronic form of the disease. A sinus or fistula formation may develop as a result of abscess progression or as a complication of a prior percutaneous biopsy or aspiration. Reactive axillary lymph nodes can be present in 28% of patients, raising the suspicion of breast malignancy [1, 3].

Mammographic findings are non-specific for IGM. Usually, IGM present as a unilateral asymmetry with or without associated architectural distortion, irregular masses may be found, coarse heterogeneous calcifications can be individualized and skin thickening may sometimes be observed [1]. Breast ultrasound is habitually performed for further characterization of lesions. Sonographic features of IGM comprise lobulated, heterogeneous, hypoechoic masses with indistinct, irregular, or angular margins and internal vascularity. Tubular extensions and posterior acoustic shadowing are often noticed. Fluid collections or abscesses may be present in 7 to 54% of cases. Skin thickening and obliteration of subcutaneous fat can also be described. On breast MRI, a T2 hyperintense-enhancing mass with or without non-mass enhancement is the most reported finding regarding IGM. Most cases express a mixed progressive and plateau enhancement kinetics. MRI can also characterize parenchymal distortion, skin changes, sinus tracts and abscess formation [1].
While there are no pathognomonic imaging features for diagnosing IGM, imaging can help document the number, location and size of lesions, thus helping to evaluate treatment efficiency and to detect eventual recurrence of the disease. Ultrasound may guide therapeutic aspirations as well as intralesional therapies.

Considering clinical similarities between IGM and breast cancer and given the non-specific findings on imaging techniques, as in our patients, histological examination remains the gold standard for IGM diagnosis. Because of the low sensitivity of fine-needle aspiration cytology in terms of IGM diagnosis, percutaneous needle biopsy has been widely used. At the microscopic level, IGM is distinguished by central non-caseating granulomas formed by epithelioid cells and Langhan's multinucleated giant cells. Chronic inflammation signs may be observed with an infiltration of polymorphonuclear leucocytes, lymphocytes and plasmacytes. Micro-abscesses are also found. It is crucial to point the absence of identification of microorganisms by bacterial staining, the absence of caseous necrosis and the occurrence of lesions mainly in the lobules rather than the ducts are key points to differentiate IGM from tuberculous mastitis [3]. Histological examination of the samples also allows other differential diagnoses of IGM (which are summarised in table 1) to be ruled out [1].

Table 1: Differential diagnosis of IGM [1]

- Cystic neutrophilic granulomatous mastitis
- Inflammatory breast cancer
- Infectious mastitis
- Bacterial
  - ✓ *Corynebacterium* species, especially *C. kroppenstedtii* and *C. tuberculostearium*
  - ✓ Periductal mastitis
  - ✓ Actinomyces abscess
- Tuberculous mastitis

- Leprosy
- Cat scratch disease
- Fungal
  - ✓ Histoplasmosis
  - ✓ Cryptococcosis
  - ✓ Coccidiomycosis
- Protozoal
  - ✓ Schistosomiasis
- Diabetic mastopathy
- Autoimmune
  - Vasculitis
  - Wegener's granulomatosis
  - Giant cell arteritis
  - Takayasu's arteritis
  - Churg–Strauss syndrome
  - Breast sarcoidosis
  - Crohn's disease
- Foreign body granulomas
  - Silicone, paraffin, PAAG injections, and beryllium IgG4-RD mastitis

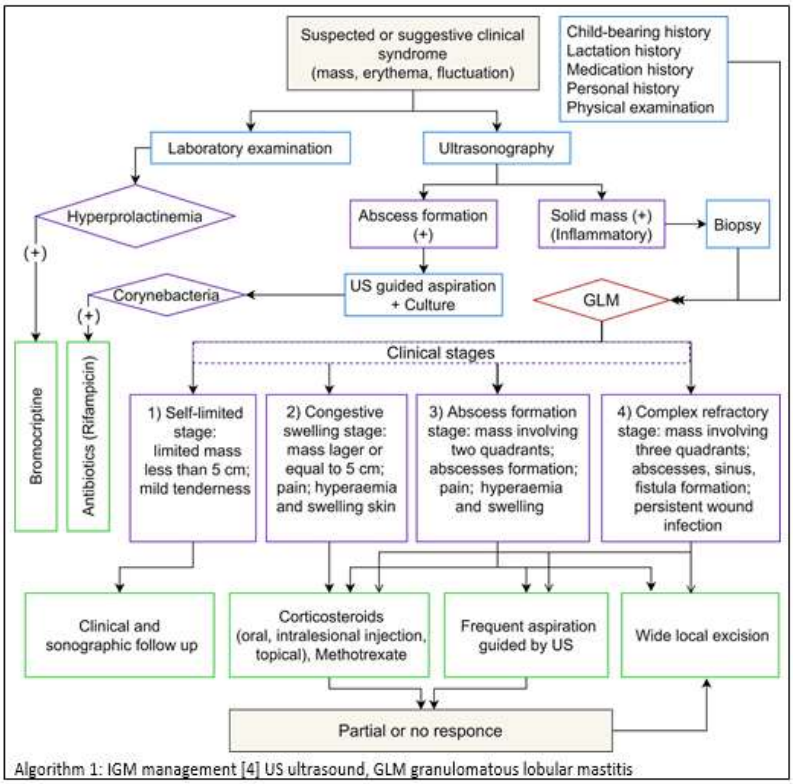
In the few previous years, a significant advancement in the treatment of IGM has been made. We currently have a long list of therapeutic choices ranging from follow-up observation to various medical treatments such as steroids, immune modulators like methotrexate and antibiotics, to abscess drainage and surgical resection. However, there is still little consensus on IGM treatment strategy. Given this controversy regarding IGM treatment choices, *Yulong et al.* conducted a review of IGM-related literature published in *PubMed* and *Web of Science* databases from 1997 to 2020, for the purpose of providing the basis for rational treatment of this disorder. Table 2 outlines their main findings [3]. In an attempt to unify the therapeutic approach to IGM, in 2021, a group of 66 international experts met and drawn up 30 very evidence-based recommendations of great interest, 10 of which relate to its treatment (algorithm 1) [4].

Table 2 : Treatment options for IGM [3]

Therapeutic options	Indications	Advantages	Disadvantages
Expectant management	Mild cases, such as small (1–2 cm) and single lesions.	1. No side effects. 2. Simple implementation.	1. A long waiting period is required (6–22 months). 2. Propensity for relapse.
Antibiotics	Adjuvant treatment against abscess, fistula or sinus formation.	Relieving inflammatory symptoms.	Lack of etiology support.
Surgery	1. Severe cases, especially large lesions (≥5cm). 2. The remedy option for steroids therapy failure. 3. The combination treatment after steroids therapy. 4. Recurrent cases.	1. One of the most effective measures. 2. Quick relief on symptoms.	1. Wound complications. 2. Esthetics challenge. 3. Recurrence is still possible (even up to 25%).
Steroids therapy	1. Applicable in most cases. 2. The initial treatment option.	1. The most commonly used therapy. 2. Effective and reliable. 3. Flexible route of administration. 4. It can be used in combination with other therapeutic options.	1. Steroids-related side effects, such as osteoporosis and Cushing's syndrome. 2. Long-term treatment (3–6 months) and good compliance are required.
Immunosuppressants	1. Failure or recurrent cases after steroids and surgical treatments. 2. Combined use with steroids treatment.	1. Powerful immunomodulatory effects. 2. Reducing the steroids dose and shorten the duration of medication. 3. Preventing recurrence during steroid dose reduction or withdrawal	1. Non-negligible side effects. 2. Lack of enough clinical supportive evidence.

Recently, intralesional and topical steroids have become the medical treatment of choice regarding IGM with similar outcomes to oral steroids. In fact, in a prospective randomized controlled study, *Yildirim et al.* enrolled 36 female patients who had been

histopathologically diagnosed with IGM and who had been randomized into two sub-groups that would be treated with systemic and intralesional steroids respectively [5]. The follow-up of the patients was performed up to 6 months and it was determined that there was no statistically significant difference between local and systemic steroid groups in terms of complete clinical regression, treatment side effects rates and recurrence rates [5]. Çetin et al. carried out a similar study, 124 patients with a histopathologically proven diagnosis of IGM were divided into three groups: patients were treated with topical steroids in group 1, systemic steroids in group 2 and combined steroids in group 3 [6]. The study concluded that the efficiency of the treatment was similar for all groups, both clinically and radiologically [6]. Although the duration of therapy was longer in topical steroids group, the lack of systemic side effects increased the compliance of the patients with this therapy [6]. A Chinese team also conducted a prospective trial to evaluate feasibility and safety of ductal lavage [7]. Intraductal infusion of corticosteroids and antimicrobial agents were performed one day and the patients returned the next day for a breast massage, this cycle was repeated for 2 weeks [7]. The research team found that ductal lavage significantly reduced the visual analogue score, 93.8% of patients achieved complete response within a median follow-up of 15.6 months and no adverse events were observed [7]. It is crucial to acknowledge that if oral corticosteroid therapy is opt for, it would be advisable to select high dose prednisolone (50 mg for three days, 25 mg for the next three days and then 12.5 mg for further three days and 5 mg daily afterwards) since it has higher success rate in the IGM treatment with lower recurrence rate and could reduce the need for surgery [8]. Indeed, our patients benefited from high dose prednisolone therapy with progressive reduction (80 mg daily for one week, with weekly reductions of 10 mg per day, over a total treatment period of 8 weeks) combined with antibiotic therapy based on amoxicillin - clavulanic acid. We have observed complete clinical and radiological regression within an average duration of 8 months and no recurrence was noted at an average duration of 32 months follow-up. While medical management is currently considered the first-line treatment of IGM, surgery is reserved for secondarily infected or refractory cases given poor wound healing, high risk of recurrence and poor aesthetic outcomes. Indeed, a meta-analysis including a total of 71 studies with 4735 patients was conducted by *Fattahi et al.* with the aim of defining recurrence factors of IGM [9]. The overall recurrence rate was 17.18%, with recurrence rates for treatments as follows: surgery (22.5%), immunosuppressive treatment (14.7%), combined treatment (14.9%), antibiotic treatment (6.74%), and observation (9.4%) [9]. Only antibiotic and expectant treatments had significant differences in recurrence rates compared to other treatments [9].



Algorithm 1: IGM management [4] US ultrasound, GLM granulomatous lobular mastitis

Conclusion

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic, inflammatory disorder of the breast which can mimic malignancy. Indeed, IGM is difficult to distinguish from breast cancer, both clinically and radiologically. Anatomopathological examination remains the gold standard for positive and differential diagnosis, revealing non-caseating granulomas and micro-abscess formation centred on the breast lobules. IGM is not only a diagnostic challenge, but also a therapeutic one. In fact, the aetiopathogenesis of IGM is poorly understood and its treatment is therefore only symptomatic and not consensual. Nevertheless, recent evidence suggests a superiority of medical treatment over surgical resections which are correlated to poor wound healing, high risk of recurrence and poor aesthetic outcomes. Oral, intra-lesional or topical corticosteroid therapy remains the first-line option for treating IGM.

References

[1] Dilaveri Christina, Degnim Amy, Lee Christine, DeSimone Daniel, Moldoveanu Dan & Ghosh Karthik (2024): Idiopathic Granulomatous Mastitis. The Breast Journal https://doi.org/10.1155/2024/6693720

[2] Chandanwale S, Naragude P, Shetty A, Sawadkar M, Raj A, Bhide A, et al. Cytomorphological Spectrum of Granulomatous Mastitis: A Study of 33 Cases. Eur J Breast Health 2020; 16(2): 146-151

[3] Yulong Yin, Xianghua Liu, Qingjie Meng, Xiaogang Han, Haomeng Zhang & Yonggang Lv (2021): Idiopathic Granulomatous Mastitis: Etiology, Clinical Manifestation, Diagnosis and Treatment, Journal of Investigative Surgery, DOI: 10.1080/08941939.2021.1894516

[4] Yuan et al. Military Medical Research (2022) 9:20. https://doi.org/10.1186/s40779-022-00380-5

[5] Yildirim Emine, Kayadibi Yasemin, Bektas Sibel, Ucar Nese, Oymak Aysegul, Muzaffer Er Ahmet, Senturk Adem & Akgun Demir Isil (2021): Comparison of the efficiency of systemic therapy and intralesional steroid administration in the treatment of idiopathic granulomatous Mastitis. The Novel Treatment for Granulomatous Mastitis. Ann Ital Chir, 2021; 10 - June 21 pii: S0003469X21035193

[6] Çetin Kenan et al. (2019) World J Surg: Comparison of Topical, Systemic, and Combined Therapy with Steroids on Idiopathic Granulomatous Mastitis: A Prospective Randomized Study. https://doi.org/10.1007/s00268-019-05084-x

[7] Kai Chen, Liling Zhu, Tingting Hu, Cui Tan, Jian Zhang, Minhua Zeng, Shunrong Li and Erwei Song. Journal of surgical research, March 2019 (235) 440-446. Ductal Lavage for Patients With Nonlactational Mastitis: A Single-Arm, Proof-of-Concept Trial. https://doi.org/10.1016/j.jss.2018.10.023

[8] Majid Montazer, Maryam Dadashzadeh & Seyed Ehsan Mousavi Toomatari. Asian Pac J Cancer Prev, 21 (4), 993-996. Comparison of the Outcome of Low Dose and High-Dose Corticosteroid in the Treatment of Idiopathic Granulomatous Mastitis. DOI:10.31557/APJCP.2020.21.4.993

[9] Asieh Sadat Fattahi, Ghasem Amini, Fatemeh Sajedi & Hassan Mehrad-Majd. The Breast Journal (2023). Factors Affecting Recurrence of Idiopathic Granulomatous Mastitis: A Systematic Review. https://doi.org/10.1155/2023/9947797