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Idiopathic Granulomatous Mastitis. Case Report and Literature Review

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Abstract

Granulomatous mastitis is a benign inflammatory pathology of the breast with an estimated incidence of 2.4 per 100,000 women. Its etiology remains hypothetical and there is no consensus on its management. **(**1**)** It is characterized by an inflammatory response with the formation of granulomas. It is currently a diagnosis of exclusion. Definitive diagnosis is confirmed by histopathology. **(**2**)**

We present the case of a 29-year-old woman undergoing a late surgical puerperium while breastfeeding, who presented with an enlarged right breast, with erythema and hyperthermia in the upper outer quadrant compared to the contralateral breast. No nipple retraction, bilateral galactorrhea, not foul-smelling. Empirical treatment was started for PM without improvement, so a mammary US was requested with a BI-RADS 4 result, with a biopsy reporting acute and chronic xanthomatous mastitis, with a positive culture for Staphylococcus aureus resistant to clindamycin. Extended right partial mastectomy and immediate reconstruction with local flaps was performed, which reported a fibrinoid and mixed inflammatory background **(**acute and chronic**)** with a predominance of polymorphonuclear cells, macrophages and plasma cells with the presence of few coccoid microorganisms. Negative for neoplasia. Ziehl Neelsen stain negative for microorganisms. A search of PubMed, Cochrane Library, Science Direct and OVID was performed. 20 articles and 1 book with greater relevance to the case were selected.

Key words: Granulomatous mastitis, mastitis, inflammatory diseases of the breast, lactation, breast abscess.

Abbreviations

Granulomatous mastitis **(**GM**)**,

Ultrasound **(**US**)**,

Centimeters **(**cm**)**,

Puerperal mastitis **(**PM**)**.

Introduction

Granulomatous mastitis (GM) is a benign inflammatory pathology of the breast with an estimated incidence of 2.4 per 100,000 women. Being a rare pathology, its etiology remains hypothetical and there is no consensus on its management. (1,3) It was first described in 1972 by Kessler and Wolloch and since then multiple articles have been published associating this pathology with elevated hormonal states, autoimmune diseases, diabetes, genetic factors, among others. (2). It is characterized by an inflammatory response with the formation of granulomas that correspond to an organization of mature mononuclear phagocytes that are sometimes associated with necrosis or infiltration of other inflammatory leukocytes. (2).

It is currently a diagnosis of exclusion considering autoimmune diseases, breast infections and carcinoma within its differential diagnoses. A thorough evaluation and high diagnostic suspicion are required to exclude other causes. (2,4) However, the definitive diagnosis is confirmed by histopathology. (2,5)

Methodology

A search of PubMed, The Cochrane Library, Science Direct and OVID was performed. Due to the low prevalence of this condition, articles and book chapters were included, in English and Spanish, less than 5 years old with the keywords: granulomatous mastitis, mastitis, inflammatory diseases of the breast, lactation, breast abscess. Systematic reviews, case reports, recommendation guides and controlled clinical trials with evidence-based medicine methodology, particularly those referring to idiopathic GM, were included. 20 articles and 1 book were selected for their relevance to the mentioned pathology and similarities with the case. Book reference is included describing associated pathophysiology.

Clinical Case

We present the case of a 29-year-old patient, gestation 1 cesarean section 1, undergoing late surgical puerperium on May 15, 2021 secondary to lack of progression of labor. No personal history relevant to the current condition. The current condition began 1 month prior to admission (June 2021) in the breastfeeding period when the right breast presented with increased volume, with the presence of erythema and hyperthermia in the upper external quadrant compared to the contralateral breast. No nipple retraction, bilateral galactorrhea, not foul-smelling. He went to the treating doctor who started an empirical antibiotic scheme with dicloxacillin without improvement of the symptoms. Breastfeeding was discontinued and treatment for puerperal mastitis was escalated to cefixime 400 milligrams every 24 hours for 7 days without improvement.

A breast ultrasound **(**US**)** was requested, reporting a heterogeneous lesion of 56x40x70 mm with a volume of 86 cc with central and peripheral enhancement on Doppler BI-RADS 4 **(**see figure 1**)**. Due to ultrasonographic findings, a core needle biopsy was performed with histopathological results of acute and chronic xanthomatous mastitis, with positive culture for Staphylococcus aureus resistant to clindamycin. She was sent to infectology who began management with Cephalexin 1 gram every 8 hours without improvement, so she was scheduled for drainage of the breast abscess with immediate reconstruction. Extended right partial mastectomy with immediate reconstruction with local flaps is performed, finding a tumor of approximately 10 centimeters **(**cm**)** of fibrous capsule which is punctured, obtaining purulent secretion **(**see figures 2 and 3**)**, which is reported in an intraoperative study: acute and chronic inflammatory reaction with no data of macroscopic malignancy. It was sent for a definitive study which reported a fibrinoid and mixed inflammatory background **(**acute and chronic**)** with a predominance of polymorphonuclear cells, macrophages and plasma cells with the presence of few coccoid microorganisms. Negative for neoplasia. Ziehl Neelsen stain negative for microorganisms **(**see figure 4 and 5**)**.

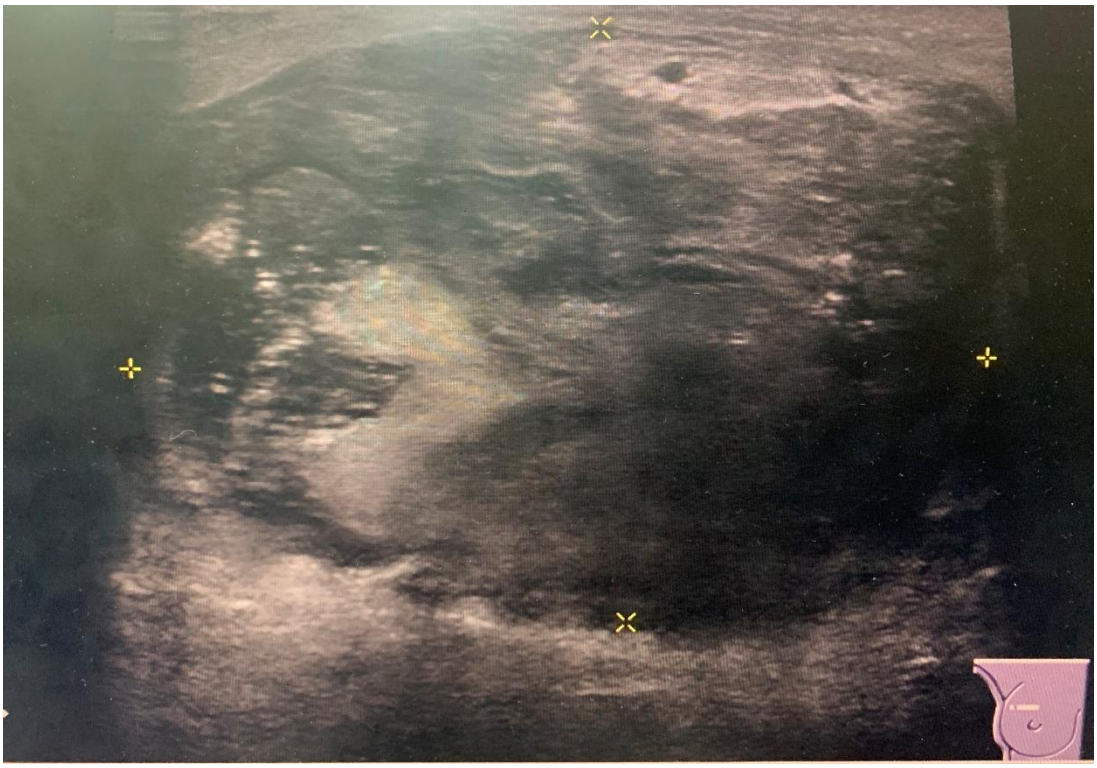

Figure 1: Breast US with heterogeneous lesion in the upper outer quadrant of the right breast measuring 56x40x70 mm with a volume of 86 cc with central and peripheral enhancement on Doppler BI-RADS 4

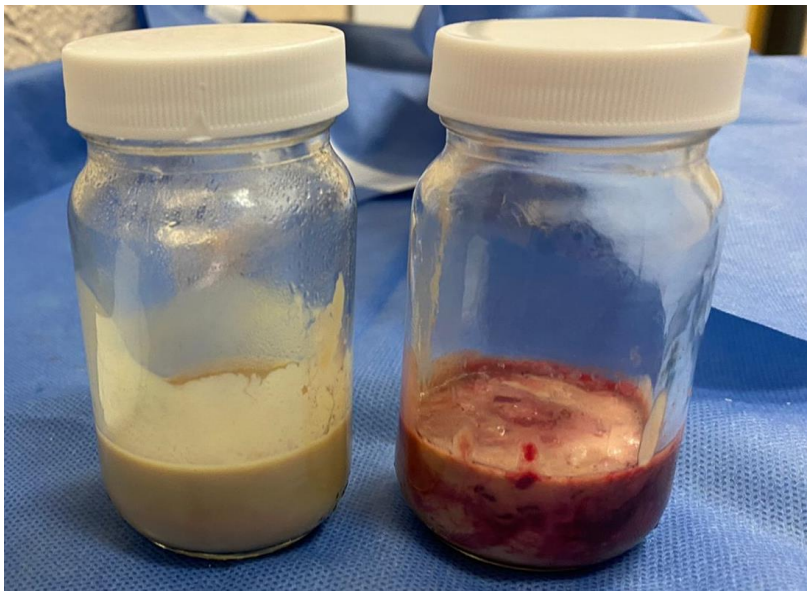

Figure 2. Right mammary tumor content.

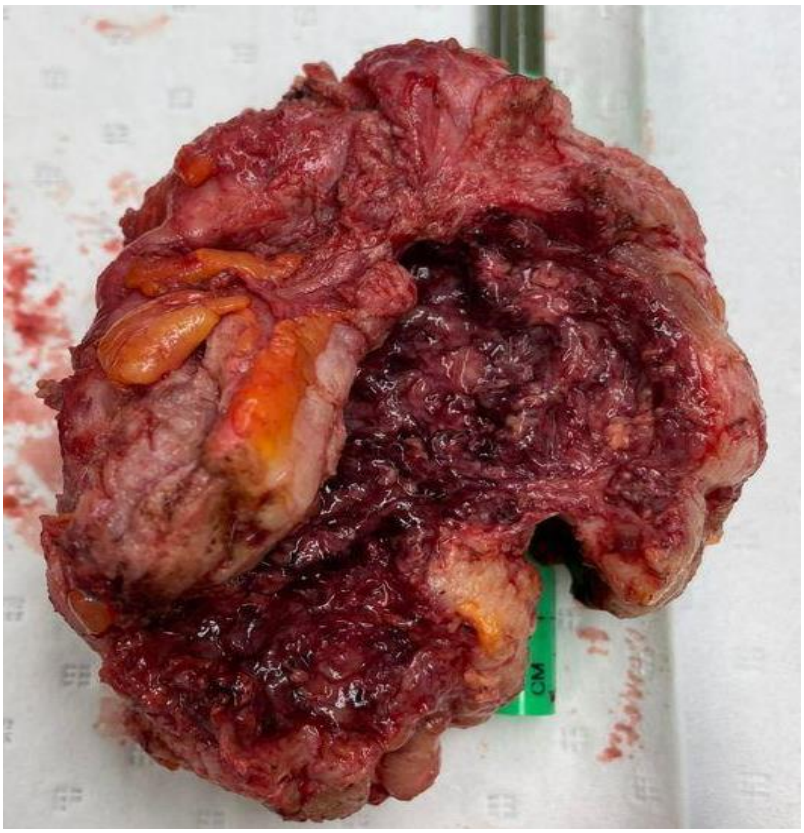

Figure 3. Capsule of right mammary lesion.

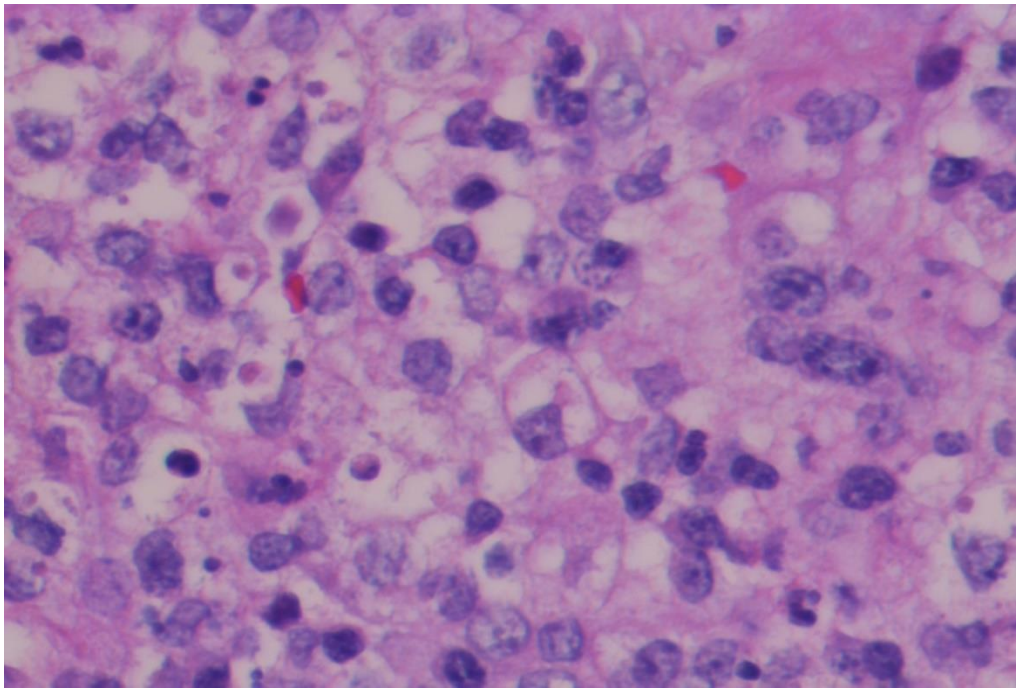

Figure 4. Mixed **(**acute and chronic**)** fibrinoid and inflammatory background with predominance of polymorphonuclear cells, macrophages and plasma cells with the presence of few coccoid microorganisms.

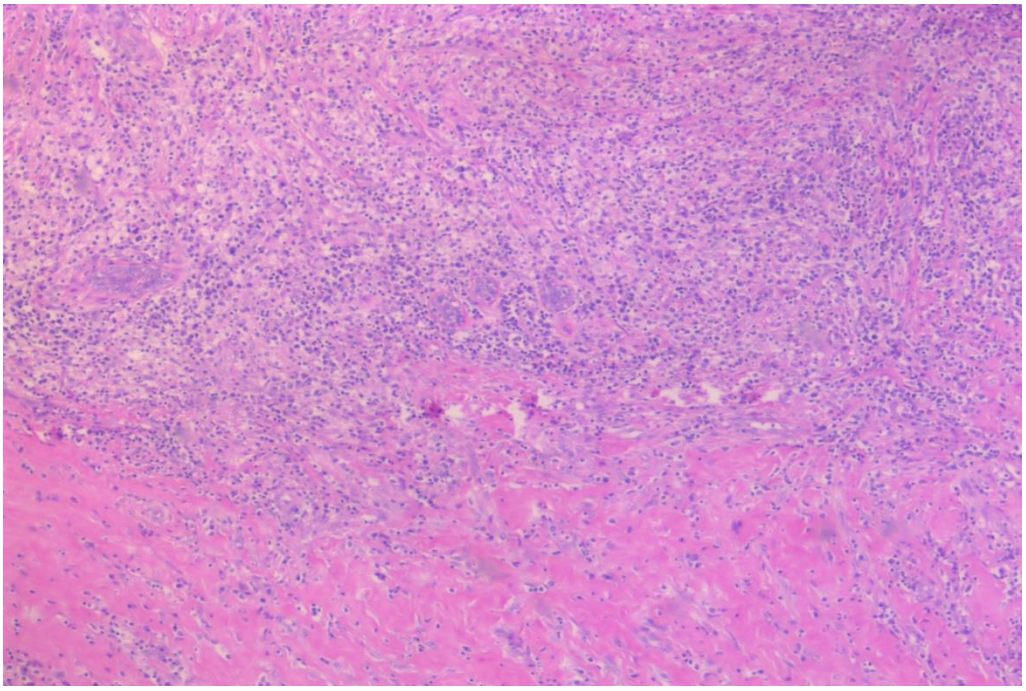

Figure 5. Granuloma formation **(**organized collection of mature mononuclear phagocytes associated with necrosis or infiltration of inflammatory leukocytes**)**

Discussion

Mastitis is an inflammatory condition of the breast usually associated with lactation and to a lesser extent with pregnancy. It can progress from a non-infectious state to infectious mastitis, with an incidence during the lactation period of 3 to 20%, and in those cases associated with lactation, it usually occurs in the first 12 weeks postpartum **(**6**)**.

It is classified according to its degree of proliferation and its association with the risk of developing breast cancer **(**7**)**. Their classification is described in the following table:

Type of lesion	**Subtype of lesion**	**Relative risk of breast cancer (95% CI)**
Non-proliferative	Simple cyst Mild hyperplasia **(**typical**)** Apocrine papillary changes Fibrocystic changes Of infectious origin: mastitis and granuloma	1.17 **(**0.94-1.47**)**
Proliferative without atypia	Fibroadenoma Intraductal papilloma Moderate hyperplasia **(**typical**)** Sclerosing adenosis Radial scar	1.76 **(**1.58-1.95**)**
Atypical hyperplasia	Atypical ductal hyperplasia Atypical lobular hyperplasia	3.93 **(**3.24-4.76**)**
Lobular carcinoma in situ		6.9-11

Table 1. Breast lesions and risk of breast cancer **(**7,8**)**

Diagnosis and management of benign breast disorders. Practice Bulletin No. 164. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2016;127:e141-56.

Pérez Sánchez VM, Meneses García A, Cano Sánchez CH, Juárez Sánchez P, Maldonado Martínez A, de la Garza Salazar JG, et al. Criterios patológicos y moleculares. In: Meneses García A, de la Garza Salazar JG, Juárez Sánchez P, Aguilar Ponce JL, editors. Lesiones benignas de la mama. 1st ed. Ciudad de México: PyDESA; 2017. p. 11–50.

Inflammatory lesions of the breast or mastitis derive from the response to certain traumatic or infectious agents, or both, whether local or systemic. It is divided into acute mastitis that frequently occurs in the first 3 months postpartum **(**75 to 95%**)**, its diagnosis is clinical and it is usually unilateral; and non-puerperal mastitis in which different mammary alterations are found, such as GM and ductal ectasia, surgical, traumatic or autoimmune complications. In this type of mastitis, its association with cancer must always be ruled out. **(**7**)**.

Puerperal mastitis (PM):

Is the most frequent complication during lactation, with an incidence of 11.1 episodes per 1000 weeks of lactation, with a peak in the first four weeks. **(**9**)**. It presents with erythema, edema, hyperthermia, and pain and may be accompanied by systemic symptoms such as fever, chills, malaise, myalgia, and lymph node involvement. It is secondary to milk stasis; during lactation sucking can cause painful erosions, the pain in turn leading to incomplete emptying and stasis in the mammary alveoli. As a consequence, there is an increase in intraductal pressure and the milk penetrates the connective tissue, breaking the intracellular junctions of the ductal epithelium, creating an initially sterile inflammation. This inflammation usually follows a bacterial infection secondary to nasopharyngeal organisms from the baby, the most frequent causative agent is Staphylococcus aureu, seguido de Staphylococcus aureu meticilino-resistente, Streptococcus pyogenes, Staphylococcus epidermidis, Stretococci viridans, Corynebacterium among others**).(**9,10**)**

Its diagnosis is clinical, and imaging studies are only requested in cases of severe disease, refractory symptoms or palpable mass. The first-line study to request is US. Treatment initially consists of continuing breastfeeding and increasing the frequency of voiding on the affected side, breast massage, nonsteroidal anti-inflammatory drugs for analgesia and antipyresis, hot compresses, and adequate hydration. If there is no improvement in symptoms within 12 to 24 hours, start antibiotic therapy, dicloxacillin 500 milligrams every 6 hours for 7 to 14 days as first line, and in case of intolerance to penicillin, cephalexin 500 milligrams every 6 hours **(**6,9,11**)**.

Breast Abscess

It presents as a palpable, painful, fluctuating mass, accompanied by clinical signs and symptoms of mastitis. In these cases, culture should always be sent and an antibiogram requested. Treatment consists of previously mentioned breast hygiene measures and suction or surgical drainage and continued antibiotics according to the antibiogram. **(**6,9**)**.

Granulomatous mastitis

Benign inflammatory disease of the breast characterized by multinucleated giant cells and granulomas limited to the mammary lobules with micro-abscesses. **(**3**)** It affects women of reproductive age between 17 and 42 years and during the puerperium, with a median age of 36.5 years, and most patients have a history of breastfeeding. **(**12**)**

theories of its pathophysiology, which focus on three mechanisms: autoimmune, hormonal and infectious. **(**12**)** It does not have a recognized etiological factor, so it is usually a diagnosis of exclusion. has been associated with Corynebacterium spp and Mycobacterium tuberculosis. **(**7**)**

It is thought to be the result of a localized autoimmune response to the extravasated fat and protein in the ducts. Within the etiological theories, infectious agents or foreign material have been associated, which trigger an immune response that leads to the formation of granulomas. And it is associated with hormonal changes since most cases occur in patients of reproductive age with a history of parity.**(**2,12**)**

Clinically it presents as a mammary lump and mastalgia, more than 50% present erythema and edema, 16 to 52% of patients present with abscess formation, it is usually unilateral and almost always affects one of the quadrants, and approximately 15% associated with ipsilateral lymphadenopathy associated with the inflammatory reaction. Most of the cases reported in the literature report that it occurs for the first time in patients in the reproductive stage, during lactation. **(**1,3,7**)**

Before concluding the diagnosis, the first contact physician most often initiates a cascade of treatment starting with empirical antibiotics.**(**1**)** Usually the condition does not resolve after antibiotic administration, and the first diagnostic modality in all groups of age is US, in which the most frequent findings are irregular contiguous hypoechoic tubular lesions with posterior acoustic shadowing with Doppler hypervascularity, 15 to 55% present reactive axillary nodes and collections and fistula formation may coexist. The next radiological modality is mammography, in which regional asymmetry is observed, and finally, magnetic resonance imaging, which shows poorly delimited hyperintense heterogeneous masses on T2 with or without central abscess formation. **(**1,12,13**)**

The main differential diagnoses include malignancy, ductal ectasia, diabetic mastopathy, Wegener's granulomatosis, mammary sarcoidosis and foreign body granuloma formation. **(**14**)**

Within the findings by cabinet methods, more than 90% are reported as BIRADS 4, making diagnostic confirmation by taking a percutaneous core needle biopsy essential. **(**15**)** The gold standard in diagnosis is the histopathological study that is characterized by non-caseating granulomas. **(**16**)**

There is no consensus regarding treatment, so there are various treatment modalities, and they will be individualized according to the degree of the injury, the general condition of the patient and the nature of the symptoms. Given that GM is sometimes self-limiting, an acceptable proposal has been surveillance in patients with mild symptoms without abscess formation. **(**12**)**

Within the proposed medical treatment, non-steroidal anti-inflammatory drugs are preferred for analgesia. Bromocriptine has been used effectively in cases with a concomitant hyperprolactinemia state. The use of oral steroids currently constitutes the first line of treatment, and in cases of early diagnosis of GM, they can potentially prevent invasive surgical treatment. Additionally, it should be considered as first line in patients who reject surgical treatment. **(**12**)**

Steroids have been used in topical, oral and intralesional presentation. The most studied is in oral presentation, with doses of 1 mg/kg/day of prednisone for 2 to 6 months or methylprednisolone 5 to 60 mg daily from 1 week to 24 months.

The main drawback with steroids is the adverse effects associated with prolonged regimens. **(**1,16**)** Intralesional steroids are an alternative treatment, in doses of 10, 20 or 40 mg at weekly intervals depending on the size and focus of the lesions. **(**17**)**

A randomized clinical trial was conducted evaluating the efficacy of low-dose prednisone **(**5 mg/day**)** versus high-dose prednisone **(**50 mg/day for 3 days, then 25 mg/day for 3 days, 12.5 mg/day for 3 days, followed by 5 mg/day**)** for 2 months. Patients were followed up 2, 3 and 6 months after treatment, observing recurrences of 37.5% in the low-dose group and 0% in the high-dose prednisone group with a p of 0.04 using chi square. **(**18**)**

Immune modulators such as methotrexate have also been used in patients who are resistant to steroid use or who develop steroid-associated complications. The dose used is 10 to 15 mg per week increasing to 20 to 25 mg per week orally or subcutaneously. **(**12**)**

Surgical interventions are considered first line in patients who require rapid remission of symptoms. Surgical excisions have proven to be successful, however, they have a high risk of recurrence of up to 50%, causing extensive scarring, delayed healing and fistula formation. They are usually the first choice in lesions that cover 50% of the breast tissue in which medical treatment has not been successful. **(**12**)**

Fewer recurrences have been seen in cases with the use of oral steroids 2 to 5 days before and after surgical treatment, versus cases with surgical treatment or the use of steroids. **(**19,20**)** Gómezpedroso-Rea et al suggest a combined technique starting 5 mg of prednisone daily for 2 weeks prior to surgery in order to reduce the size of the lesion and achieve a better cosmetic appearance, with recurrences in less than 10% of cases. **(**16**)**

Conclusion

Granulomatous mastitis is a diagnostic challenge. Due to its morphology and presentation, the diagnosis should always be confirmed by histopathology, in turn ruling out the existence of a carcinoma. Its management is controversial due to its low incidence and little knowledge of its pathophysiology, in addition to the fact that its prevalence is in areas of low socioeconomic level. The current trend is to start with oral steroids prior to surgical management, since they tend to recur and become complicated, potentially requiring multiple surgical interventions. However, cases with fewer recurrences have been observed in patients with combined surgical and steroid management.

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