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Original Research

Idiopathic Granulomatous Mastitis- Where Do We Stand

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Abstract

Granulomatous mastitis is a rare benign disease with chronic inflammatory features. Its diagnosis relies on a characteristic histological pattern, combined with the exclusion of other possible causes of chronic inflammatory lesions in the breast. It can occur between 0.025% and 3% of all breast diseases treated surgically. Only a few hundred cases had been reported in the literature and its treatment had been modulated from observation only, to multiple modality medication treatments and or extensive surgical treatment including mastectomy, with minimal or no changes of management. We present our experience of 31 cases diagnosed granulomatous mastitis managed according to a tailored treatment algorithm. This is an observational study with a comparison to new data consensus for management. Our results suggest oral corticosteroid treatment remains a good alternative for management. Further adjustments of algorithm to include proper differential diagnosis and new treatments are to be established.

Key words: Granulomatous Mastitis; Chronic Inflammation; Steroids

Material and methods

31 successive cases of granulomatous mastitis diagnosed by biopsy in our breast unit from Jan 2012 to June 2023, were analyzed retrospectively; data including age, history, triple assessment, various radiologic and laboratory data, treatment approach, recovery, and recurrence were evaluated.

Imaging included ultrasound of breasts and mammography for patients over 40 years of age. Mammograms were performed with two standard views (mediolateral oblique and craniocaudal) of each breast and additional mammographic projections if needed.

A definitive diagnosis was confirmed by ultrasound-guided core biopsy, excisional biopsy, or from biopsy specimens taken from the abscess wall during drainage. The slides were examined by dedicated pathologists with hematoxylin-eosin and specific stains, such as Gram, Ziehl-Nielsen, and periodic acid–Schiff/ Grocott stains; the study included only proven noncaseating granulomatous mastitis cases with other possible causes of granuloma formation having been addressed clinically, radiologically and histopathologically.

Tuberculosis had special attention to differential diagnosis, though appropriate testing was not performed routinely.

Management consisted of observation only, antibiotics, steroids, incision and drainage, multiple aspiration and, surgical excision. Antibiotics given included a range of broad-spectrum penicillin, cephalosporins, and tetracyclines.

Steroid treatment, when given, was a prednisolone loading dose of 30 mg per day, single daily administration for 3 to 4 weeks initially, followed by weekly 5mg taper down to a maintenance dose of 5mg daily for 3-6 months, or more. No immunosuppressants were used in our series.

The recovery period was defined as the time between the initial office visit and the disappearance of the symptoms. Recurrence was defined as the reappearance of the same symptoms after their initial disappearance.

The patients were followed up in the outpatient breast clinic, and those who recovered and no longer visited the office were followed up via phone interviews. The data that were collected were then studied and the various parameters were compared retrospectively.

Results:

The average age of the patients was 36 years (ranging from 24 to 48 years old). All our cases were females and premenopausal. 3 out of 31 cases were diagnosed while not married, with no children, the rest of 29 being within 1-4 years of childbirth, lactating (2 cases), or pregnant (2 cases). 14 cases out of 31 had other co-morbidities implying hormonal imbalance such as polycystic ovaries, diabetes mellitus, thyroid dysfunction, miscarriage, hyperprolactinemia, or oral contraceptive use. 1 case was on prolonged use of heavy antidepressants.

The most common presenting symptom was a lump in the breast- 26 out of 31 cases. Most of the patients had inflammatory symptoms of pain, many having signs of redness. 4 patients had pus discharge through the skin; 4 cases had clinically identifiable ipsilateral lymphadenopathy. 29 cases were unilateral, and only 2 cases bilateral, which had a protracted course with the need for multiple aspirations or surgical drainage.

Image-wise, Ultrasound was performed in our unit in 30 of the cases. Half of the cases had at least micro abscess formation. Serial ultrasound imaging averaged 4 times on follow-up, ranging from 0 ultrasounds (2 cases diagnosed in another facility) to 11 ultrasounds. The range of Ultrasounds implied multiple aspirations done in the radiology department with close follow-up. About a third of our cases were aspirated in the Breast Clinic, 2 cases necessitating multiple aspirations.

Mammography was performed in 7 cases out of 31 cases, all being over 35 years of age. Mammography showed ill-defined tumor in 4 out of 5 cases when done, 1 case having asymmetric density.

3 patients out of 31 had MRI of breasts with contrast - two cases for recurrence and one other case upon the protracted clinical course. No MRI was done as initial imaging.

Two cases had free hand biopsy of breast mass, 29 cases ultrasound-guided biopsy with or without aspiration in the same setting, according to the assessment.

The histopathology specimens were of idiopathic non-caseating granulomatous mastitis and were accessed through the histopathology database. Specimens were obtained by core biopsy or by surgery. There were 8 cases specified as cystic neutrophilic granulomatous mastitis and one polarized foreign body reaction granulomatous mastitis.

Ziehl-Neelsen stains were performed in 24 cases on biopsy specimens- all negative. Gram stains upon biopsies, also 24 cases, brought the attention of gram-positive rods in 3 cases, one of them specified as Corynebacterium species, and, 2 cases with Gram-positive Cocci, not otherwise specified.

Wound culture was performed in 21 cases with no growth in all cases; AFB culture was done in 12 cases, from wound culture or biopsy specimen; only 1 AFB positive culture was identified, congruent to one of the 3 Tuberculous granulomatous mastitis cases, which were not included in our group.

7 cases underwent surgical incision and drainage-, out of which only one had the second surgery with excision of abscess wall due to protracted course. 4 cases that underwent incision and drainage had a persistent fistula formation sorted by steroid treatment.

4 cases underwent excisional biopsy, 3 of them as initial diagnosis workup, done in another facility; 1case upfront excision biopsy was done in our facility for a breast lump increasing in size with unexpected histopathological diagnosis of granulomatous mastitis. It was completely removed. This case had no sign of recurrence postoperatively.

Special testing of exclusion, such as Chest X-ray was done in 14 cases- all negative for TB. T spot was done for 9 patients, out of which 6 patients were negative, 2 were equivocal and 1 case was positive. The positive T spot, case was assessed and diagnosed as latent TB with known exposure and unrelated non-specific granulomatous mastitis.

Other immunological testing done- ANA, rheumatoid factor, Anti DNA, thyroid function tests, etc., were related to the multiple comorbidities that the patient presented with.

All of our cases had at least one course of antibiotics- ab initio- Cefuroxime, Amoxicillin-Clavulanic acid, tetracycline, or lincosamide class. Antibiotic courses ranged from 1 course to 5 courses, a mean of 2 courses before another type of treatment ensued.

There were 12 patients out of the 31 cases that are documented to have received corticosteroids. The course of treatment had variable responses, according to initial findings, compliance to treatment, most of them with partial or total resolution. 10 out of 12 cases had had minor adverse effects of weight gain, being the biggest drawback subjectively, resulting in poor compliance. The other known side effects of corticosteroid treatment such as changes in mood, muscle weakness, growth of hair, bruising, etc., went unnoticed.

10 cases were observed clinically without administration of steroids, but with initial multiple aspirations until settled or, onsetting the steroid treatment on a flare-up. 7 cases are unaccounted for due to loss of follow-up.

Follow-up itself done by USS which assessed the evolution, developments, and resolution.

The mean follow-up period after the first attack was 42.4 months (range 1–60 months) . The resolution was determined with the disappearance of hypoechoic lesions or with the stability of hypoechoic lesions for more than 6 months when applicable. The clinical course had a variable swaying in between periods of regression to another flare-up. In 21 out of 25 followed-up cases were observed with a clinical regression course at 2 years. 4 cases had a recurrent course. These cases initially necessitated aspiration and/or a prolonged course of steroids.

Discussion:

Since the concept proposed by Miller et al., in 1971 [1], and the description by Kessler and Wolloch in 1972 [2], knowledge of this disease and its management is still evolving. In 2011 the term cystic neutrophilic GM was coined by Renshaw as a subtype of GM [3]. Due to the rarity of the disease and its self-limitation, cases are scarce, therefore difficult to study, and difficult to nail up one single conclusion or a standardized practice. The literature search reveals small studies, the highest being a couple of hundred cases in one study spanning many years. New RCTs or meta-analysis of idiopathic granulomatous mastitis brings up to 970 cases in one comparative study [4], concentrating on comparison between different modalities of treatment, be it surgical, medication, and their combination or route of administration- steroids,

immunosuppressants, antibiotics-, or be it observation only. The term *mammary duct–associated inflammatory disease sequence* was introduced by Meguid and colleagues, resulting from obstruction, distention, inflammation, and rupture of the lactiferous ducts as an initial trigger, allowing luminal secretion to escape into the lobular connective tissue, where it stimulates a granulomatous response and further damage the lobular structures. fueled by a particular immune background [5].

As a chronic inflammatory disease, granulomatous mastitis has two forms: idiopathic or attributable to specific infections (tuberculosis, fungal, parasitic, brucellosis, filariasis, and actinomycosis) or specific noninfectious causes such as autoimmune diseases-(sarcoidosis, Wegener's granulomatosis, diabetes mellitus; alpha-1 antitrypsin, rheumatoid arthritis, Behçet disease, erythema nodosum), or varia such as trauma, foreign body reaction, fat necrosis or plasma cell mastitis, or iatrogenic hormones, none of them being proven directly involved [5,6].

Dubai Hospital's Breast Unit addresses patients from different ethnical backgrounds. The majority of our presented cases are of Arabic origin followed by 2 cases of African origin, 2 cases of Subcontinental origin, and 4 cases of far east, reflecting the demographics of the population served and the cases of benign disease. All our cases are triple-assessed and managed in a multidisciplinary setting. Our series of 31 female cases is spanning over 11 years. As reflected in the literature, the majority of our cases are associated with hormonal imbalances of some sort, yet not all have a history of childbirth and one case has had symptomatic hyperprolactinemia. No routine testing was done for prolactinemia.

The serological immune tests that were done were all negative, not being able to point out a direct implication.

It is important to underline the presence of endemic cases of tuberculosis from nearby countries with the inherent difficulty of diagnosing differentially TB versus granulomatous mastitis. Breast tuberculosis accounts for less than 0.1% of all known breast diseases globally but it comprises up to 3% of treatable breast lesions in developing countries., Gulf area 0.4-0.5% [7].

Our study has 3 additional cases, which, although diagnosed as non-caseating granulomatous mastitis, in the context of their clinical presentation from an endemic area and with biological correlation were treated as breast tuberculosis and responded completely to anti-tuberculous specific drugs from their country of origin.

Clinically GM presented most commonly as a unilateral mass with or without inflammatory features. The majority of our cases complained of pain of different degrees associated with the mass. The majority of cases are more than 5cm in size, one-third of them with abscesses formation and skin involvement, and very few with sinuses formation or occupying more than 2 quadrants of the breast. According to the new consensus for staging- most of our cases were staged II, and III [8].

The literature describes up to 15 % of associated lymphadenopathy [9]. Our cases were mostly considered reactive ipsilateral axillary lymph nodes. As of note, the literature identifies arthritic pain in 4.6% of cases [10]. Our study included 2 patients out of 31, at 6.4% with joint pain. One of the cases was referred to immunology for possible reference treatment with immunosuppressant but the patient refused.

Imaging: no pathognomonic imaging was described in the literature; Han et al. described multiple small masses or a large focal asymmetric density. The most common finding is an irregular ill-defined mass. [11,12].

Most of our patients had ultrasound imaging as an upfront assessment. As per protocol, all patients over 40 years of age had mammography at the initial presentation. Most of the images were consistent with literature of ill-defined mass with multiple small collections/abscesses or branching.

Histopathology: The difficulty of clinical presentation whether malignancy, specific or non-specific granulomatous mastitis was eased by triple assessment, and core biopsies or surgical biopsies were performed in all of our cases with no FNAC done.

For the patients that had an image of abscess, the collection itself was aspirated and a sample was given to microbiology labs for studies of AFB, fungal and bacterial growth. Some patients had had multiple aspirations according to clinical progress. The core biopsy samples were subjected to special stains such as Ziehl Nielsen for TB elements, Grocott Methamine Silver stain, and periodic acid Schiff stain for fungal organisms, all of which were negative.

Labs: In the attempt to differentiate nonspecific granulomatous mastitis from tuberculosis in a clinical setup, more tests were performed. The literature considers Chest X-ray, tuberculin skin test, determination of erythrocyte sedimentation rate, and PCR helpful with the diagnosis [13,14].

Given the multinational hub with a statistically increased number of patients coming from originally endemic tuberculosis areas, in our practice, we have to include, and, in fact, constantly have to beware of differential diagnoses of TB. However, a pathway in the diagnosis of it is very much needed given the fact that treatment is exclusive and opposing granulomatous mastitis management. When tuberculosis is considered as a differential diagnosis there are certain drawbacks.

The histopathologic examination requires the specimen to be placed in formalin, which destroys the mycobacteria and prevents further culture confirmation. Biopsy material for mycobacterial culture is submitted fresh or in a small amount of sterile saline and even so, the conventional smear microscopy has a low sensitivity with a range of 0%-40%, and negative results cannot exclude the presence of TB. The reported yields of mycobacterial culture vary from 30% up to 80%. It usually takes 2-8 weeks to receive the results, which is too slow to help treatment decisions.

In our study, we found it difficult to identify through additional tests even if patients are coming from endemic areas of tuberculosis.

The Nucleic acid amplification tests (NAAT) such as polymerase chain reaction (PCR) are rapid and specific but suffer from low sensitivity, especially in AFB smear-negative cases which are represented by all of our cases. Sensitivity has been reported in some series as low as 62% [15]. A negative NAAT result does not exclude TB disease with certainty.

The Tuberculin skin test and serology are of limited diagnostic value given that adults from TB endemic areas are expected to have high rates of positivity for these tests.

The blood tests QuantiFERON-TB Gold In-Tube and T-SPOT TB use interferon-gamma release assays (IGRA) to detect people with tuberculosis and are useful, especially for diagnosing latent TB. QuantiFERON-TB Gold In-Tube had a pooled sensitivity for active TB of 81% and specificity of 99.2%, whereas T-SPOT.TB had a pooled sensitivity of 87.5% and a specificity of 86.3% [16]. The significance of these tests' positivity in the context of granulomatous mastitis is not yet established. The 3 cases that were positive for the T SPOT test in our study, were asymptomatic, chest X-rays were negative and in one case TB PCR blood was negative.

Treatment: The ideal therapeutic management of IGM is eluding. Histopathological confirmation, combined with the exclusion of malignancy and other causes of granulomatous disease, is of great importance in guiding clinical decision-making and preventing inappropriate and unnecessary treatments. Clinical management often starts with tests to eliminate microbial infection and, when microbial infection can be ruled out, long-term oral steroid treatment or surgery is administered. It was reported that in situations where no therapy was given, almost 50% of patients had a spontaneous and complete resolution with no recurrence, but the mean time to complete resolution in 1 study was 14.5 months [17].

Observation management has a disadvantage in that it requires careful follow-up for an extended period and repeated imaging and histological tests may be needed.

The incidence of TB is higher in countries endemic for tuberculosis such as Indian subcontinent where it may be as high as 3-4%. Such countries have developed a pathway called 'Directly Observed Therapy Short Term' , where, based on the endemic presence of disease, clinically suspected TB cases even with negative lab findings are subjected to short-term trial therapy of Tuberculosis, and response is observed. 2 of our cases, originally from Indian subcontinent had TB PCR negative, were treated in their home country upfront with antitubercular medication as per standard and improved to clinical disappearance of the mass, being asymptomatic at 1½ year.

The Arabian Gulf the incidence is reported to be in between 0.4 and 0.5% as per Saudi Study [7], which is 10 times lower than in endemic areas of tuberculosis. Therefore breast specific mastitis on these values becomes difficult to consider for directly observed therapy as a standard protocol.

Empirical antibiotics was used for all of our patient's encounters based on inflammatory changes ab initio, ranging from 1 to 5 courses making it difficult to assess the effect of treatment, should the steroid treatment be ensued or overlapped. In addition, the specificity of clinical setup in our area which implies extensive private facilities along with our governmental setup is rendering patients liable to insurance and financial issues and to non-congregated means of diagnosis and or management.

There are 7 patients in our studies that had lost follow-up. And there are 3 other patients that were initially diagnosed and partially managed elsewhere.

To date, there is no, single, effective antibiotic treatment on GM. Our study had patients with multiple different courses of antibiotics. Its effect could not be directly determined in this study.

Although one of the hypotheses of GM is that infection could cause it, only one case was detected having Corynebacterium species in the biopsy culture. This bacteria is brought to light in recent studies over a new histopathological entity of cystic neutrophilic granulomatous mastitis. Our study identified 8 such cases out of the total 31.

The drawback of this Gram-positive bacilli identification relates to its saprophytic existence as a skin germ and is not usually taken into consideration by the microbiology lab for an aimed culture, prior to the diagnosis. Our study incidentally identified the germ in the biopsy itself proposing additional microbiological studies on all cultures of breast abscesses ab initio. Further studies on Corynebacterium-directed therapy are also warranted. Our case had a short clinical response to such therapy with acute flare-ups being switched to corticosteroid treatment with ongoing follow-up.

Steroid therapy, on the other hand, was reported to decrease the size of the lesion and provide complete healing when used long-term.

The disadvantage is that can exacerbate undetected underlying breast infection. Therefore, long-term use of steroid therapy is not usually possible and is recommended only for use in recurrent and refractory cases with close observation and only when an infectious etiology has been excluded.

Recently, Ogura *et al.* reported GM cases in which an infiltrate of immunoglobulin G4–positive ($IgG4^+$) plasma cells was present and speculated that patients with IgG4-related GM might benefit from corticosteroid therapy, as do those with IgG4-related autoimmune disorders [18]. If 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. More studies are needed.

Steroid use prior to excision may permit a more conservative surgery. When abscess formation is observed, drainage of the abscess should be performed before the start of steroid therapy. Oral

prednisolone is preferred for corticosteroid therapy. The literature dosage is 0.8 mg/kg/day. Our cases received oral steroids and were loaded with 30mg daily dose, 0.5mg/kg/day. Our treatment period was an average of 3 to 6 months, 2 of the cases with extensions to 8 and 9 months, respectively, and another 3 cases with flareups spanning over 3 years with different duration of treatment.

As high as a 50% recurrence rate has been reported after stopping the therapy [19]. Our study showed 8 cases out of 31 (about 25%) with flareups after ceasing the steroid over 1 to 4 years follow-up. A close follow-up allowed dose modifications when necessary. We followed out cases at 1, 3, 6, and 12 months regularly with adjustment of medication when needed.

There are new data in small series related to intralesional steroids to a good outcome. It remains to be seen its effectiveness. Similar data on topical steroids. Neither form are part of our practice at present.

Surgical treatment in the literature varies from simple incision and drainage to multidirectional deep drainage with or without a combination of antibiotics and or corticosteroids or excision up to mutilating mastectomy for protracted extensive cases. 7 of our 31 cases were dealt with in an emergency setup and underwent incision and drainage. 1 of 7 cases underwent re-surgery with excision and recovered completely.

The drainage method is still controversial in GM treatment because the incision wound does not heal easily and can leave a fistula tract, and treatment can last for an extended time. Erozgen et al. [21] reported that 14 of the 25 GM patients developed abscess and underwent drainage followed by steroid treatment, and suggested that drainage is the first choice of treatment for patients who develop an abscess. Abscess must be treated by drainage, but it is suggested that the drainage be followed by additional appropriate therapies. In our study, 4 cases had fistula formation amended by additional steroid treatment.

A third of our 31 cases underwent aspiration many of them multiple times. It is our belief that close follow-up with aspiration and medical treatment when needed has a better overall outcome than surgery in GM and every attempt should be made in that direction.

Surgical excision was considered a critical treatment method for GM when was first reported in the 1970s. It was later suggested, however, that GM should not be treated surgically to avoid complications such as fistula formation and poor wound healing. In addition, a higher recurrence rate was reported after surgical excision compared to the recurrence rate after steroid treatment. Therefore, steroids became a popular means of GM treatment [20]. Recently, however, attention is being given again to surgical treatment, with studies on this method continuing.

To ensure the success of surgical treatment, the surrounding normal tissue, the affected breast skin, the fistula, and the sinus track should be completely removed even if the lesions become localized and resectable. However, we did not encounter such cases in our study. The only excision biopsy done was performed on a small localized GM diagnosed postoperatively with an uneventful outcome. We do not support excision based on reports of misdiagnosed carcinoma. Every effort should be made for an appropriate diagnosis before formal surgery.

Because the natural history of GM is supposed to be self-limiting, our experience indicates that close surveillance with multiple aspirations and minimally required surgical procedures might be the first-line treatment of GM. Recurrence, fistula formation, and secondary infection are well-known complications of idiopathic GM, thus long-term follow-up is recommended.

As such, the first multidisciplinary consensus of 2021, China, brings in a useful algorithm that emphasizes multimodality diagnosis and management in different stages of the disease [8].

Our management algorithm includes triple assessment, biopsy for mass formation, aspiration or incision and drainage with culture, oral steroid

for abscess-, close follow-up, further course of steroids, or possible further surgery on relapse or protracted course, reflecting a combined modality treatment.

New studies and consensus [8] bring in the need of incorporating clinical stages in our practice, prolactin assessment for all our cases, Corynebacterium specified cultures with lipophilic antibiotics targets, stratification of various modalities of treatment according to the stage and prospective evaluation of intralesional steroid treatment to possibly alleviate side effects of oral steroid treatment.

Conclusion:

Granulomatous mastitis is a rare benign breast disease that must be diagnosed in a multidisciplinary approach. Each case of GM should be evaluated separately, and the appropriate treatment modality in a specified algorithm should be chosen according to patient and disease characteristics.

Increased awareness of this disease will improve its understanding and management.

The side effects of corticosteroid treatment may be challenging in such a benign disease. Though, overall, close follow-up with multiple aspirations and oral corticosteroid treatment is the proposed modality of choice in GM in our view, with minimalization of any formal surgery, a systematic approach evidence-based algorithm is a must. Other treatment modalities such as intralesional steroid administration are yet to be established.

Conflict of interest: none

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