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Diopathic Granulomatous Mastitis: A Multifaced Approach

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ABSTRACT

Idiopathic granulomatous mastitis remains one the most mismanaged benign breast disease due to the difficulty in its diagnosis. As it closely resembles breast cancer as well as tubercular and pyogenic breast abscess, surgeons often excise the lesion or drain the abscess as soon as possible. This leads to an increase in recurrences and causes significant disfigurement. Patients are often distressed, in chronic pain and have massive financial burdens due to repetitive surgical procedures, given the waxing and waning course of this disease. Hence, a standardized multidisciplinary approach is required to effectively treat the disease with minimal relapses and recurrences..

Keywords: *Idiopathic granulomatous mastitis, Breast, Benign, Mastitis*

1. INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a benign, chronic inflammatory disease of the breast which was first described by Kessler and Wolloch in 1972.[1] The disease classically presents as a unilateral breast lump or an abscess in parous women of the reproductive age group. The aetiology, natural course and treatment of choice of this condition are not yet well understood. Due to the rarity of the condition and the lack of sufficient studies, the prevalence of IGM is not known.[2] Baslaim et al. in their study reported that IGM represents 1.8% of 1106 cases of benign breast disorders which were subjected to a biopsy.[3] Histopathology and radiology findings often suggest periductal mastitis. In fact, some authors consider it to be a variant of periductal mastitis.[4,5]

Possible predisposing factors of IGM include lactation disorders that result in milk stasis, hyperprolactinemia, smoking, OCP use, alpha-1 anti-trypsin deficiency, Corynebacterium infection (cystic neutrophilic granulomatous mastitis) and blunt trauma to the breast.[6-10] Milk stasis plays a key role causing the breast tissue to hypertrophy subsequent to pregnancy, lactation, and hyperprolactinemia. Pituitary adenoma, antipsychotic drugs (such as potent D2 receptor antagonists, risperidone), and antidepressant drugs (selective serotonin reuptake inhibitors like fluoxetine) can lead to hyperprolactinemia.[11,12] While the permeability of breast ducts increases (by physical or chemical trauma), its immunogenic contents (retained milk) enter into lobular mesenchyme of the breast, causing T cell-mediated immune response which results in granuloma formation.[13] It may also lead to a B cell mediated immune reaction which causes extramammary manifestations such as inflammatory arthritis, arthralgias, episcleritis, and erythema nodosum.[14] It is not clear in the literature how oral contraceptives are predisposing factors.[15]

It has also been proposed that IGM may result from damage to the ductal epithelium due to chemical or infectious stimuli which may lead to fat extravasation and ultimately granulomatous response with migration of macrophages and lymphocytes to the breast tissue.[17]

2. MATERIALS AND METHOD

A retrospective study of patients with IGM was conducted in Chettinad Hospital (a Tertiary Care Centre) from 2018 to 2023. Patient sample size was 11. Inclusion criteria comprised of patients with breast lump and/or breast abscess which was proven to be IGM by histopathological examination (FNAC, core needle biopsy or an excisional biopsy). The disease was surgically managed with lumpectomy, an incision and drainage (in case of an abscess), excisional biopsy or a wide local excision as required. Medical management was done with prophylactic antibiotics (oral and topical), topical steroids, NSAIDs and opioid analgesics.

We staged the disease based on Yuan QQ's classification:

- Stage 1 (Self-limited) - One or more masses less than 5 cm with minimal pain and tenderness. No abscess formation, skin changes or axillary lymphadenopathy will be present. During this stage, GLM can be regarded as "white skin mass stage".
- Stage 2 (Congestive swelling) - Masses of 5cm or more with pain, swelling and hyperemia. It is therefore regarded the "red skin mass stage".
- Stage 3 (Abscess formation) - Includes masses involving 2 quadrants, breast abscess formation, pain, swelling and hyperemia usually accompanied by axillary lymphadenopathy in acute phase.
- Stage 4 (Complex refractory stage) – Comprises of mass involving 3 quadrants with abscesses, sinus, fistula formation and persistent wound infection.

3. RESULTS

After compiling patient records, laboratory investigations, radiological imaging and surgical notes, we report:

- 2 patients with breast lump
- 4 patients with breast abscess and
- 5 patients with co-existing unilateral breast lump and abscess at the time of presentation.

Based on Yuan QQ's staging, we had: one patient with stage 1, two patients with stage 2, six patients with stage 3 and two patients with stage 4 disease. Mean age of our study group was 36 years, ranging from 20 years to 58 years. Ten of our patients were parous and had breastfed their children, out of which two patients were lactating at the time of presentation of the disease. Base characteristics of our study subjects are enumerated in Table 01.

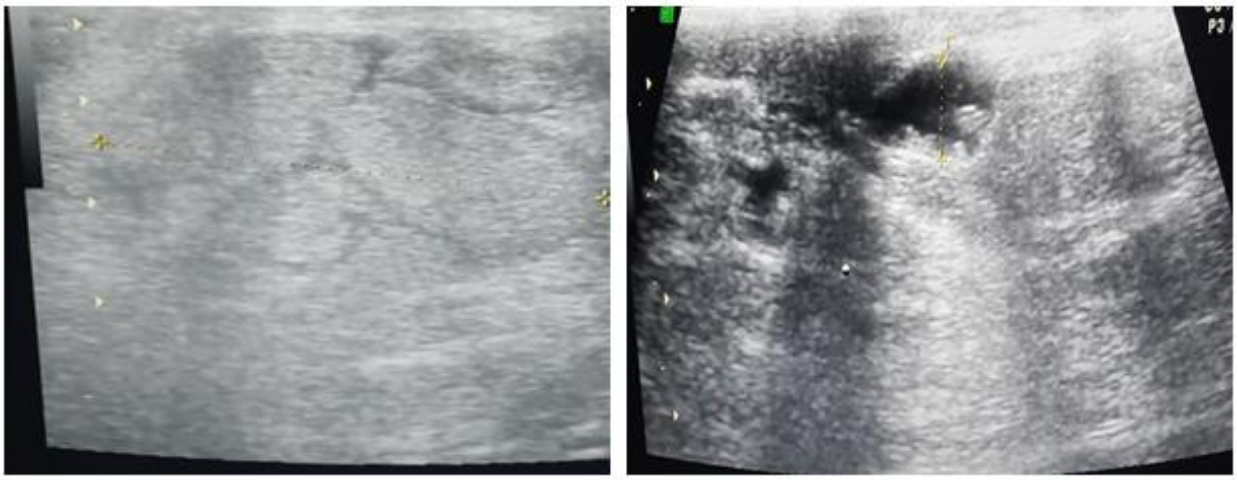
TABLE 01: Base Characteristics of the Study Population

Characteristics	Percentage
Breast lump	18%
Breast abscess	36%
Breast lump and abscess	45%
Recurrences	36%
Parous	90%
Lactating	27%
Post-menopausal	18%
Diabetes	27%
Hypertension	9%
Oral contraceptive use	9%

Clinical signs and symptoms included breast pain (prickling pain which was insidious in onset and intermittent in nature)-100%, high grade fever (36%), axillary lymphadenopathy (9%), nipple discharge (mostly serous or serosanguinous) – 18%, induration, nipple retraction (18%), skin ulcers (9%) and peau d'orange (9%). While the largest breast lump removed was 12*10 cm, the mean size of the lesions from our study group was 7*6.5 cm. Left sided involvement was seen in 7 patients, right sided disease in 3 patients and 1 patient had bilateral disease. Four of our patients had recurrences; 3 had same sided recurrence while the fourth had bilateral recurrence. None of our patients reported any menstrual irregularities or endocrine

disorders.

Three of our patients were diabetic and consuming Oral Anti-hyperglycaemic agents; out of which one patient was a 58-year-old post-menopausal woman who was diabetic and hypertensive with bilateral involvement classified under stage 4. The disease recurred thrice from 2020 to 2022. She underwent 3 surgeries; a core needle biopsy in 2018 initially, her first recurrence in 2020 was conservatively managed; her second recurrence was managed with a left sided drainage and right sided excisional biopsy in 2021 and her third recurrence was managed with right sided excision and biopsy in 2022.



A (B)

Figure 01: Stage 4 disease in a 58 year old patient.

(A) Right breast – Hyperechoic lesion; (B) Left breast – Hypoechoic lesion with abscess formation

Our second patient was a 33-year-old diabetic woman consuming OCPs. She presented in 2022 with a chronic abscess on her right breast (which was drained) and left sided fibro-adenosis affecting all quadrants of the breast. Post-operatively, she has been experiencing early morning stiffness, body pain and intermittent low-grade fever for the past year, however the patient was unwilling to test for rheumatoid arthritis. Meanwhile the third diabetic patient was a 50-year-old nulliparous woman with a retro-areolar abscess and lump. Nipple retraction, whitish nipple discharge and peau d'orange were also noted. She underwent an excisional biopsy and was prescribed topical corticosteroids. Based on our findings, we deduce that diabetes mellitus seems to aggravate the severity of this disease causing a wide variety of manifestations with increased recurrences. It is hypothesized that sustained hyperglycaemia results in the accumulation of advanced glycosylated end products, which are highly immunogenic and may favour cytokine production, B-cell lymphocyte proliferation, and matrix remodelling, all leading to breast inflammation.[17] Limitation – Our sample size was small.

Ultrasound was the investigation of choice and it revealed extremely invasive, ill-defined and heteroechoic lesions showing diffuse Brownian movements. Periductal mastitis and duct ectasia were seen with multiple echogenic ducts which were filled with ectatic material. Colour doppler showed increased vascular uptake around the lesion.

A 38-year-old patient with left sided stage 3 disease (lesion sized 5*4 cm), contracted Covid-19 pre-operatively due to which her surgery was postponed by a month and she was managed conservatively. She subsequently developed left axillary lymphadenopathy, which resolved on its own post-operatively. The course of her disease did not have any significant variations due to her Covid positive status.

(A) (B)

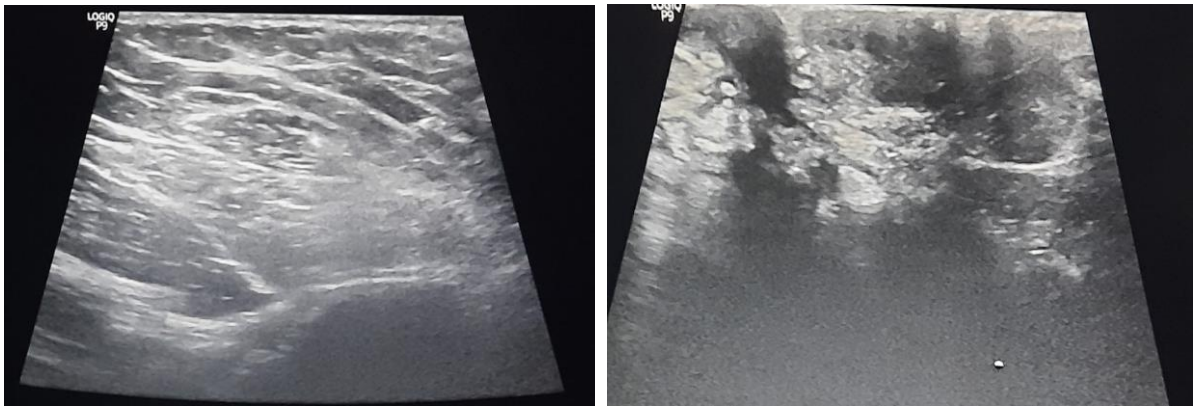


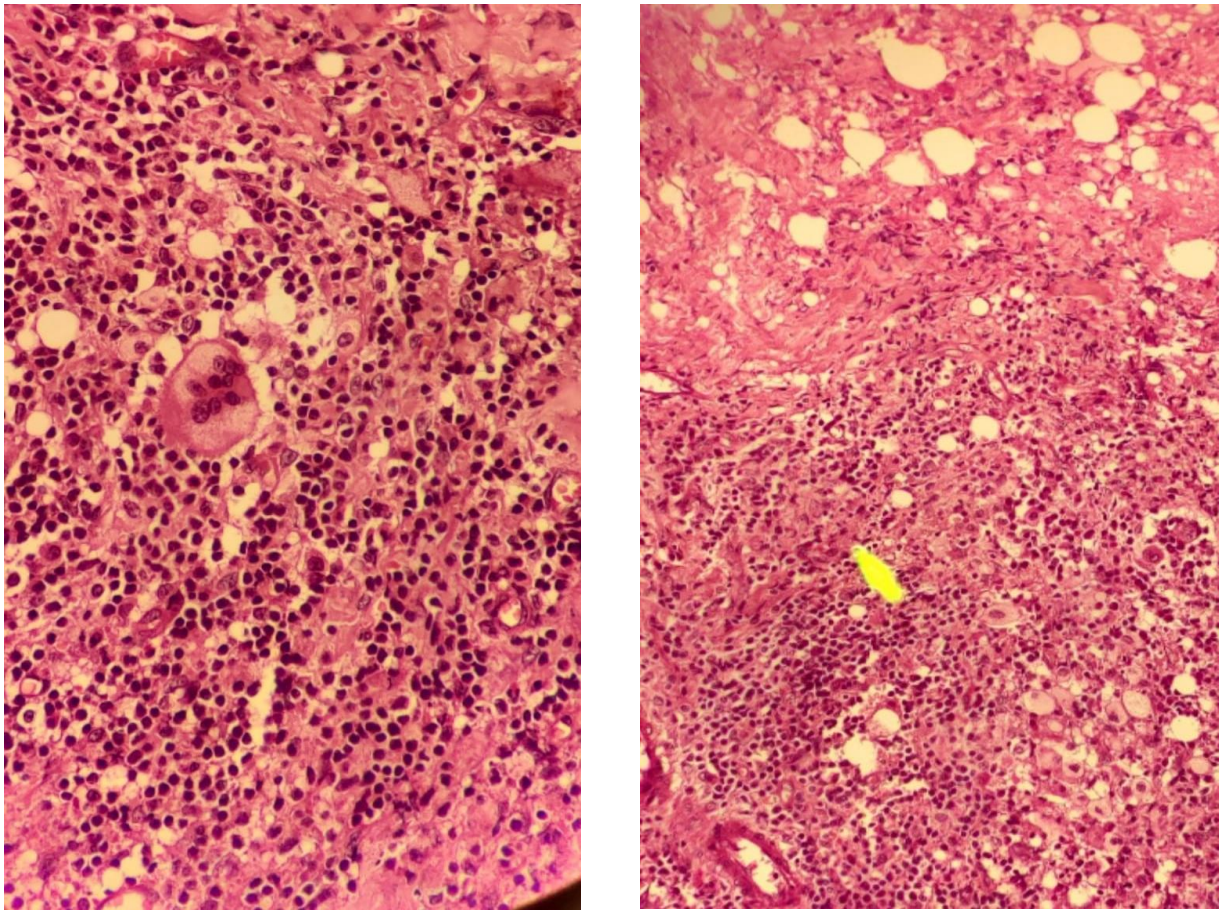
Figure 2 - Stage 4 disease of left breast in a 33-year-old patient.
A) Duct ectasia with inspissated material B) Heteroechoic lesion sized 12*10 cm

Histopathological examination (HPE) by FNAC (2/11), core needle biopsy (3/11) or excisional biopsy (6/11) of all patients revealed non-caseating granulomas, xantho-granulomatous reactions with areas of fat necrosis, epithelioid cell granulomas, multi-nucleated giant cells, foamy histiocytes and Langhan's giant cells in the lobules. Ducts were dilated, ectatic and filled with cholesterol clefts and proteinaceous material. Periductal inflammation and stromal fibrosis was also noted. The surrounding tissue is mainly infiltrated by neutrophils, lymphocytes, plasma cells and a small number of eosinophils. The lesions were multifocal and formed micro abscesses. Inflammation of IGM was typically confined to the breast lobules, rarely involving the main ducts.

Out of the 14 procedures performed on our 11 patients for treatment of initial disease and recurrences, the type which is denoted in Table 02. Patients who underwent incisional drainage and local excision had many recurrences compared those who underwent wide local excision. Medical management was done with oral antibiotics such as levofloxacin, cephalosporins, aminoglycosides and metronidazole before antibiotic susceptibility testing. NSAIDs and benzodiazepines were given for pain relief and sedation. We did not prescribe steroids or methotrexate for our patients as the diagnosis of IGM had not been proven. We had suspected an infectious aetiology and felt the risks of using steroids outweighed the benefits. However, one patient was prescribed topical steroids post-operatively and she reported no recurrences.

TABLE 02: Number of Surgical Procedures Performed

Surgical procedures performed	Patients	Recurrence
Incision and drainage	3	-
Local Excision	6	4
Wide local excision	1	-



(B)

Figure 3 – Histopathological images
A) Foamy histiocyte in a background of Xantho-granulomatous reaction
B) Area of fat necrosis (arrow) and xantho-granulomatous reaction

4. DISCUSSION

IGM is a very poorly understood disease seen in patients presenting with breast lump and/or abscess associated with breast pain, fever, axillary lymphadenopathy and other systemic manifestations. Due to the significant number of recurrences even after surgical management, this disease should be considered a working diagnosis with multiple treatment modalities. An international multidisciplinary consensus on the management of IGM was reached in 2021[6]. Literature from 1971 to 2020 was reviewed to provide evidence-based recommendation. Sixty-six experts from 11 countries reviewed the evidence and after extensive discussions, a consensus was reached.[6]

They recommended checking prolactin levels to rule out hyperprolactinemia as it causes milk stasis which acts as a sensitizer and induces an autoimmune reaction.[6] Apart from pregnancy and lactation, a minority of cases can be caused by:

- Dopamine antagonistic medications (anti-psychotic drugs such as metoclopramide, prochlorperazine and antidepressants like fluoxetine)
- Intracranial tumors such as pituitary adenoma and craniopharyngioma.[18] Craniopharyngiomas compress the adenohypophysis and prevent the entry of dopamine, resulting in the disinhibition of prolactin secretion.[18] Hence, Nikolaev et al. suggest screening for pituitary tumors if patients have hyperprolactinemia of unknown aetiology.[18]

Bromocriptine (dopamine agonist) can be given to reverse hyperprolactinemia, especially in patients with massive breast engorgement.[6,18] It has been reported that prolonged breast-feeding might result in long-term distension of acini and ducts; which can facilitate the rupture of these structures inducing a granulomatous response.[3,19] Baslaim et al. reports that patients who preferred to breast-feed from one side commonly developed IGM in the contralateral breast, as it had experienced sustained distension without relief.[3] There is no clear reason why some nursing mothers prefer unilateral breast-feeding, but a significant number do so, and when any breast pathology occurs later in life, it usually involves the contralateral side.[3]

Mixed microbial infections are implicated in the pathogenesis of IGM and some of these are atypical microbes, which are difficult to isolate under ordinary culture conditions.[6] Rifampicin inhibits the growth of most Gram-positive and many Gram-negative bacteria, including atypical Mycobacteria that may be involved in the pathogenesis of GLM.[6] Non-penicillin drugs such as clindamycin, levofloxacin and azithromycin can be applied empirically before the outcome of antibiotic susceptibility test just in case it is a Corynebacterial infection, as they are notoriously resistant to Beta-lactam antibiotics.[6,20]

Steroid use is widely recommended either by systemic or local routes as it decreases the disease severity and minimalizes the need for surgical management. Yuan et al. recommended the use of local steroids over systemic steroids as it is contra-indicated in pregnant, diabetic, or lactating women and has a wide variety of side effects such as weight gain, osteoporosis, and worsening infections.[6] The outcome of treatment with topical/intralesional steroids is much better as Toktas et al. proved this in their study which included 78 women with IGM.[6,21] They found that recurrence rates in patients treated with local steroids (both topical and intralesional) was 8.7%, yet 46.9% of patients given peroral steroids experienced disease recurrences.[21] Need for further surgical management was 2.2% and 9.4% in patients receiving local and systemic steroids respectively.[21]

However, if systemic steroids are indicated, Shojaee et al. reported a 61% cure rate with low dose oral corticosteroids combined with drainage, as high dose peroral corticosteroids and surgical excision had cure rates of only 22% and 16% each.[16] However, the recurrence rates for low dose and high dose steroids were equal at 36% and surgical excision had the lowest recurrence rate of 28%.[16]

For breast masses with single or multiple abscesses or even sinus, Xiao et al. recommended aspirating pus repeatedly, guided by USG, washing the abscess cavity using 0.9% NaCl solution, followed by injecting 40 mg triamcinolone acetonide into the abscess cavity through the aspiration needle or drainage tube. The therapeutic efficiency was 78.26% (18/23), and the effective time is (6.00 ± 2.09) days.[6,22] Ik Eom recommended 6–7 times of triamcinolone acetonide injection (maximal dose 20 mg with interval every 3 weeks). Furthermore, intra-mammary corticosteroids injection can also be administered to perilesional fibro glandular area in patients without abscess formation. The major advantage of this method is that it can be applied in multiple sessions until satisfactory results were obtained.[6,23]

Administration of corticosteroids for large lesions prior to surgery may help in obtaining better cosmesis. IGM patients with mainly skin changes or those suffering from side effects of oral corticosteroids can be treated with intralesional corticosteroid injection and topical steroids.[6] Intralesional injection and topical corticosteroids can effectively reduce the side effects, especially in patients suffering from concomitant skin lesions (e.g., mammary duct fistulas, skin erosions, ulcers).[6,24-26] Unfortunately, a lot of patients have comorbidities (diabetes, osteoporosis) or develop side effects which contraindicates any further use of corticosteroids. In such cases, methotrexate monotherapy can be given in oral or subcutaneous routes. A combination of methotrexate and corticosteroids have also proven to be beneficial due to their synergistic effect.[6,27,28] The dosage of MTX is 5–15 mg/week for 6–24 months, and patients receiving MTX should be given two doses of folic acid per week before MTX use.[6,29]

Postolova et. al performed a study with Methotrexate monotherapy and of the 19 patients they treated, 94% demonstrated notable improvement and 75% had disease resolution with the use of MTX as monotherapy.[30] Only 15.8% of patients relapsed while on treatment but continued to improve/resolve when changed to SC administration.[30] Mild side effects such as nausea and elevated liver function tests (LFTs) were reported.[30] Nausea resolved with changing route of administration from oral to subcutaneous route and LFTs normalized once drug dosage was reduced.[30] They noticed rapid and sustained responses occurring with MTX doses between 15 and 25 mg PO or SC weekly for 12 months followed by gradual tapering over an additional 6–12 months, for a total of 18–24 months of treatment.

Surgery is recommended in patients of:

i) Stage 2 disease (5 cm mass) with intolerance, treatment failure or recurrence with antibiotics, corticosteroids and methotrexate.

ii) Stage 3 disease (abscess involving 2 quadrants)- USG guided aspiration and wide local excision (as last resort) is recommended

Stage 4 disease (mass of >4 quadrants, abscess, sinuses and wound infection)- wide local excision is regarded as the mainstay of treatment in this stage.[6]

Wide local excision is mostly preferred due to a cure rate of 94.5% and a recurrence rate of 4%. Whereas the cure rate for oral corticosteroids is 90.6% and recurrence rates are 6.8%.[31]

According to Yuan et al. experts stress upon certain steps in a wide local excision for IGM –

Wound wash with 3% hydrogen peroxide, iodine and 0.9% saline after excising necrotic tissue and pus.

Changing instruments and gloves to avoid re-contamination during the reconstruction surgery.

Breast plastic surgery can be performed with the glandular fascia flap and fascia tissue.

Double-layer purse string suture at the base of the nipple makes the nipple protrude to avoid postoperative indentation.

For patients with extensive local resection, autologous tissue displacement and shaping can be performed.

Ahmed et al. recommend therapeutic mammoplasty to reduce recurrences, improve cosmetic outcome and patient satisfaction.[32] This was performed in patients with moderate to large breasts with breast mass of 20-50% of the size of the breast.[32] In patients with large breasts, they performed reduction mammoplasty to regain bilateral breast symmetry and obtain an aesthetic outcome.[32]

We found that in our institute although we promptly managed the disease, our patients had a large number of recurrences and quite a lot of disfigurement. Without confirmation that the lesion was not malignant or infective, we were hesitant to prescribe steroids or methotrexate. Hence, we recommend performing an FNAC or core needle biopsy to confirm the diagnosis and then prescribing low dose peroral steroids, topical steroids and peroral methotrexate (to be preceded by folate supplements) in case of a stage 1 or 2 lesion. In case of a stage 3 abscess, we recommend aspirating the pus and then injecting steroids into the abscess cavity, followed by topical steroids with or without prophylactic peroral antibiotics. In stage 4 we recommend injecting steroids into the lesion prior to wide excision to minimize inflammation, thereby excision and improve cosmetic outcome. In case the patient is dissatisfied with cosmetic outcome we recommend therapeutic mammoplasty.

5. CONCLUSION

Idiopathic Granulomatous mastitis remains one of the most under-diagnosed and mismanaged breast disease given that it closely resembles other benign breast diseases. Interpreting clinical and radiological findings is quite challenging, however histopathological examination of the biopsy cinches the diagnosis. Disease management requires medical management with corticosteroids, methotrexate and prophylactic antibiotics. Surgical intervention must be kept to last resort in order to avoid repetitive surgical procedures (local excision and incisional drainage) which give symptomatic relief without eradicating the underlying disease.

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