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Management of Idiopathic Granulomatous Mastitis Diagnosed by Core Biopsy: A Retrospective Multicenter Study

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■ **Abstract:** Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory condition of the breast, which usually mimics breast carcinoma. The aim of this study was to analyze the clinical features of IGM by identifying a more reliable diagnostic protocol, and evaluating the treatment methods and patient outcomes on follow-up. We performed a retrospective analysis of 46 patients diagnosed with IGM and managed by the same surgical team between 1999 and 2011, at three high-volume hospitals. The median age of the patients was 33 years. The most common symptom was painful breast mass ($n = 39$), followed by abscess ($n = 11$). All patients underwent ultrasonography (USG). Mammography (MG) and magnetic resonance imaging (MRI) were also performed in 20 patients (43%) and 17 patients (37%), respectively. The mean size of the lesions was 32.8 ± 8.8 mm and ranged from 15 to 50 mm. Preoperative diagnosis of IGM was established by core needle biopsy (CNB) under USG guidance. Eighteen patients (39%) underwent complete excision of the lesion and 25 (54%) were treated with steroids. Three patients treated with steroids subsequently underwent local excision. The mean follow-up period was 35.4 ± 30.9 months. Eight patients (17%) developed disease recurrence; three of these were successfully treated with steroids, one with surgery, and four with both steroids and surgery. CNB in conjunction with high diagnostic accuracy has a significant role in distinctive diagnosis of IGM and hence, is useful for treatment planning. Treatment can be designated according to the extent and the severity of the disease, and the patient's general health and treatment preferences. Patients with IGM must be closely followed up due to the frequency of disease recurrence. ■

Key Words: core biopsy, corticosteroid, Idiopathic granulomatous mastitis, surgery, treatment

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory condition of the breast, characterized histologically by noncaseating granuloma formation within the breast lobules and neutrophilic micro abscesses (1). IGM predominantly affects women of childbearing age and typically presents with the clinical symptoms of inflammatory breast mass (2,3). The condition is easily confused with breast carcinoma due to the nonspecificity of the clinical and radiological findings (4,5). Preoperative definitive diagnosis of IGM is therefore an important step in the planning of treatment. The disease may be locally aggressive and has a tendency to recur (6).

Different management options may be implemented; these include conservative approaches with close surveillance, mastectomy, wide excision, abscess drainage, and immunosuppressive therapy with corticosteroids. However, there is no consensus on the optimal treatment of patients with IGM (7,8).

Demonstration of granulomatous inflammation in the lobular units of the breast is required for the definitive diagnosis of IGM (1). However, establishing the correct diagnosis by excluding the malignancy and other known causes of granulomatous diseases such as tuberculosis and *Corynebacterium* infection (9–11)

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may be quite difficult. So, histopathologic diagnosis plays a very important role in the management of IGM patients. The novel biopsy techniques that can be used for the diagnosis of IGM of the breast are fine-needle aspiration biopsy (FNAB), core needle biopsy (CNB), or surgical biopsy (excisional or incisional) (1). Because surgical biopsy is more invasive and leaves a scar on the breast, it is usually considered as the last choice after FNAB or CNB has failed. FNAB may not always differentiate between IGM and other granulomatous diseases of the breast (10) and, a false-positive FNAB result may lead surgeons to a more invasive surgery (1). CNB of the breast has some superiority to FNAB, whereas CNB can more completely characterize lesions; insufficient specimens are unusual, and it does not require special cytopathology trained pathologists (12).

In this study, we report our clinical experience in the management of 46 patients diagnosed with IGM between 1999 and 2011 and review the pertinent literature. This study demonstrates that CNB provides a more reliable diagnosis of IGM, leading to a substantially higher treatment success. To our knowledge, this study comprises the largest series on this topic to be reported in the English literature.

PATIENTS AND METHODS

Our report is on 46 patients diagnosed with IGM between 1999 and 2011 and treated at three different high-volume hospitals. The patients' medical records were retrieved from Istanbul Haseki Educational and Research State Hospital, Istanbul Memorial Hospital and Namık Kemal University Research Hospital and the data were analyzed retrospectively. Diagnostic and therapeutic management of all 46 patients was undertaken by the same team (the authors of this report).

We recorded etiologic factors such as smoking, use of oral contraceptives, local trauma, time to presentation since last delivery or breast feeding, family history of breast cancer, presenting symptoms, clinical findings including size and localization of the lesion, and the presence of abscess or sinus formation. We also looked for any history of autoimmune disease.

All patients underwent ultrasonography (USG) examination (Fig. 1), and patients older than 40 years of age also underwent mammography (MG; Fig. 2). On suspicion of malignancy, magnetic resonance imaging (MRI) was performed to further investigate it (Fig. 3). All patients underwent trucut biopsy of breast lesions that presented either as a mass or as suspicious inflammatory tissue. Pathology slides were stained with hematoxylin–eosin, and with specific stains such as Gram for bacteria including *Corynebacterium*, Ziehl-Neelsen for tuberculosis, and periodic acid-Schiff for fungal infection. The stained samples and the bacterial culture were examined by two experienced pathologists. All patients showed negative results for tuberculin (purified protein derivative, PPD) skin tests and polymerase chain reaction (PCR) studies, and their chest radiographs showed normal findings, excluding the diagnosis of tuberculosis. IGM was defined as a granulomatous inflammatory reaction detected on lobules in the absence of a caseous necrosis or any specific organism (Fig. 4).

Breast abscesses were drained as an initial treatment step for patients with breast abscesses; these patients also received antibiotic therapy, as did those with positive microbiological culture, sinus formation, or breast inflammation. Patients either underwent wide surgical excision or were given medical treatment with steroids, depending on the dimensions of the lesion, the severity of symptoms, and the patient's general health and personal treatment preferences (Fig. 5). All patients were assessed by physical examination and USG on follow-up and their outcomes were analyzed.

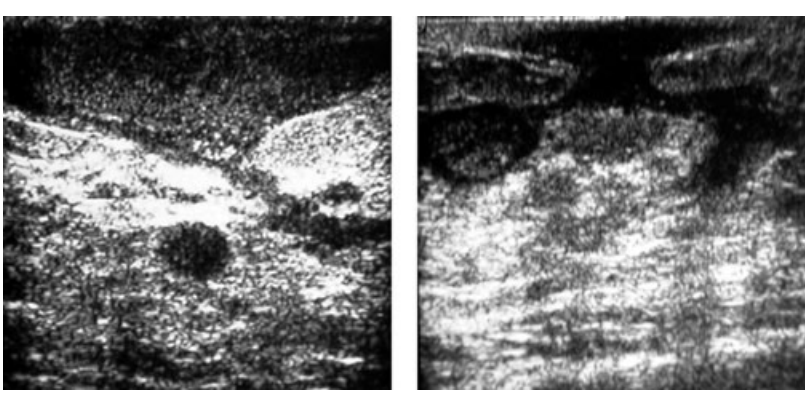

Figure 1. Increased thickness of the dermis and hypoechoic tubular fistule tracts extending to the dermis in ultrasonographic evaluations of a patient with Idiopathic Granulomatous Mastitis (IGM).

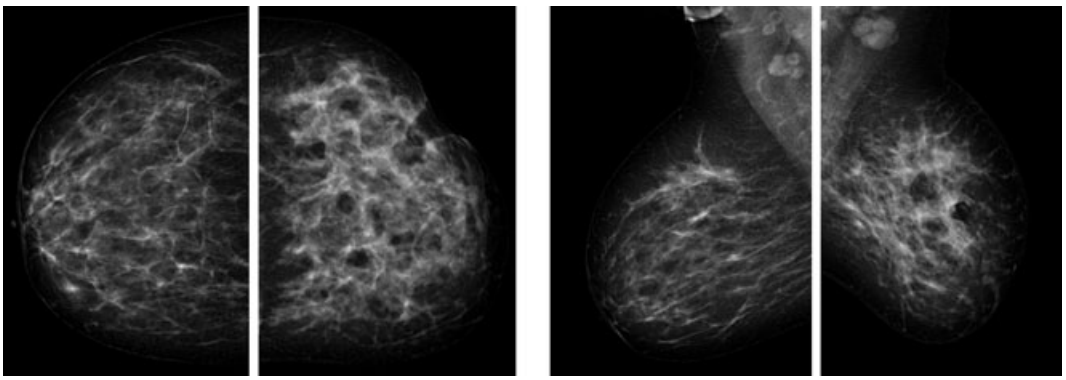

Figure 2. Diffused parenchymal asymmetry, retraction of the mamilla, enlarged axillary lymph nodes, and diffused increased periareolar thickness of left breast in CC and MLO mammographies of a patient with Idiopathic Granulomatous Mastitis (IGM).

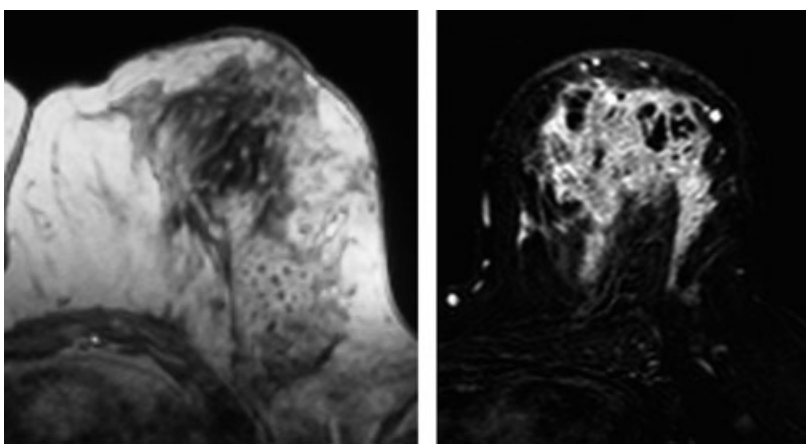

Figure 3. Magnetic resonance images showing increased periareolar thickness, microabscess focuses in outer quadrant and parencyhmal contrast enhancement indicating diffused inflammation in patients with Idiopathic Granulomatous Mastitis (IGM).

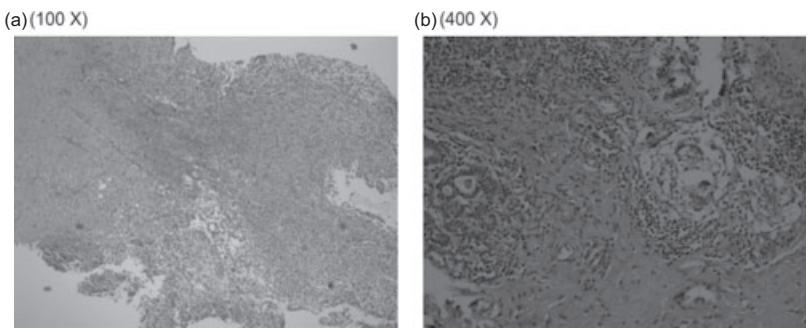

Figure 4. Granuloma formation in Hematoxylin- and eosin-stained core needle biopsy (CNB) (a) and wide surgical excised breast tissue (b) specimens of patients with Idiopathic Granulomatous Mastitis (IGM).

RESULTS

Clinical Characteristics

The clinical and demographic characteristics of the patients are shown in Table 1. The median age of the patients was 33 (range 28–55) years. None of the patients had a history of autoimmune disease or a first-degree relative with a history of breast cancer.

Painful breast mass was the most common presenting symptom (frequency, 85%, $n = 39$). Ten patients had axillary lymphadenopathy on the same side as the breast lesion. One patient presented with bilateral breast involvement. All other patients had unilateral IGM. The most frequent site of localization of the breast lesion was at the upper outer quadrant ($n = 16$, 34%), followed, in descending order, by the inferior outer quadrant ($n = 10$, 21%), the areola

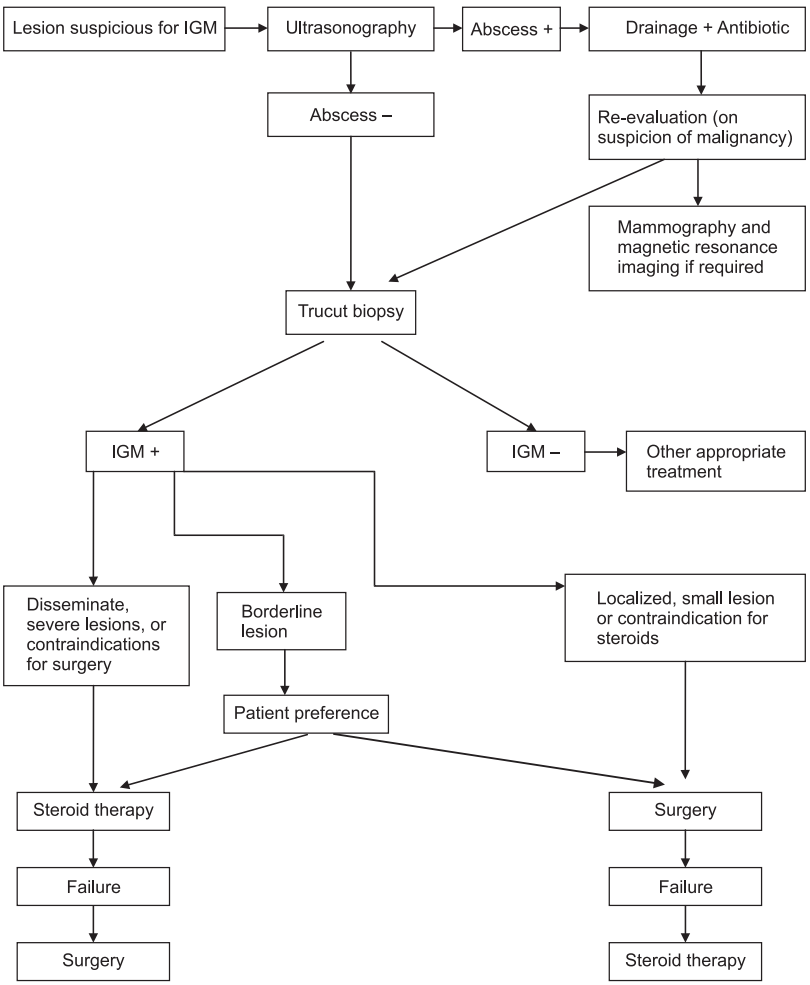

Figure 5. Flow chart for the management of suspected Idiopathic Granulomatous Mastitis (IGM) lesion of the breast.

Table 1. Clinical and Demographic Characteristics of Patients with Idiopathic Granulomatous Mastitis (IGM)

Etiologic characteristics	No. of patients ($N = 46$) n (%)
Smokers	16 (35%)
Took oral contraceptives	10 (22%)
Nulliparous	3 (6%)
Delivered or breast fed during previous year	13 (28%)
Clinical findings	
Painful breast mass	39 (85%)
Breast abscess	11 (24%)
Sinus formation	6 (13%)
Inflammatory hyperemic skin and breast tenderness	2 (4%)
Location of the lesion	
Left breast	25
Right breast	20
Bilateral	1
Mean size of the mass (mm)	32.3 ± 8.8

region ($n = 8$, 17%), the inferior inner quadrant ($n = 7$, 15%), and the upper inner quadrant ($n = 6$, 13%).

Treatment, Follow-up, and Outcomes

All 46 patients were investigated by USG; 20 patients (43%) also underwent MG and 17 patients (37%) were further investigated with MRI to ensure safe breast imaging. All patients underwent trucut biopsy for preoperative diagnosis of IGM. The incidence of granulomatous mastitis diagnosis was 2.5% among all core biopsies of breast in our study. Breast abscesses were drained as the first step of treatment in the 11 patients who had abscesses; five of these patients had positive culture test results for *Staphylococcus* species and three had positive results for *Streptococcus* species. Nineteen patients (41%) were treated with antibiotics for an average duration of 2 weeks.

Table 2 shows the treatment allocation in patients with IGM. Eighteen patients (39%) underwent complete excision with negative margins for the inflammatory granulomatous tissue, and 25 patients (54%) were treated with steroids (Fig. 6). The standard dose

of steroids, 16 mg prednisolone twice daily for 2 weeks, was administered, and thereafter, the dose was slowly tapered and the therapy stopped 6 weeks later. Four patients received steroid therapy for 12 weeks. Three patients (7%) who failed to respond to steroid therapy subsequently underwent local excision. There were no severe side effects related to steroid treatment.

The median follow-up period was 35.4 (range 3–135) months. Eight patients (17%) developed disease recurrence. The median time to identification of recurrence was 5 months in patients treated surgically and 7 months in those treated nonsurgically. All except one patient presented with recurrence in the same quadrant in which the primary lesion had been identified. Three patients originally treated with surgical excision developed a recurrence; of these, one patient responded positively to steroid therapy and two patients underwent repeat excision followed by steroid treatment. Five patients initially treated with steroids had recurrent disease; of these, two patients responded positively to a second course of steroid therapy, one was successfully treated by local excision, and in two patients, there were no regression by initially used second course of steroids, so later, they were also treated by local excision. The patients' outcomes are given in Table 2.

Table 2. Treatment and Follow-up Outcomes in Patients with Idiopathic Granulomatous Mastitis (IGM)

Patients ($N = 46$) n (%)	Treatment	Disease recurrence (n)	Management of recurrence
18 (39%)	Surgical excision	3	Steroid therapy ($n = 1$) Excision + steroids ($n = 2$)
25 (54%)	Steroid therapy	5	Steroid therapy ($n = 2$) Steroids + excision ($n = 2$) Surgical excision ($n = 1$)
3 (6%)	Steroid therapy + surgical excision	None	None

DISCUSSION

Idiopathic granulomatous mastitis is a chronic inflammatory benign condition of unknown etiology (1). It is rare, generally affects young women under 50 years of age, and is frequently associated with recent pregnancy and lactation (1,2,8,13). Almost 30% of the patients we studied had a history of delivery and breastfeeding within a year before presentation. Taylor et al. (11) postulated that extravasated lactation secretions may be responsible for eliciting a granulomatous inflammatory response in the lobular connective tissue. Local trauma, autoimmune processes, or chemical agents, such as oral contraceptive drugs and smoking, may cause extravasations of luminal content with induced ductal epithelial damage (1,4,6,14–16). One third of our patients were smokers and 22% had a history of oral contraceptive use.

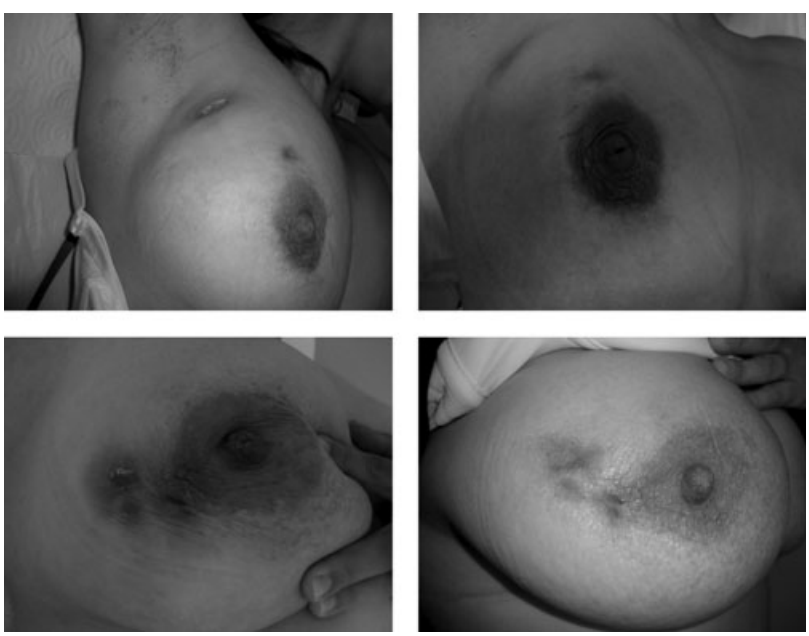

Figure 6. Breasts with Idiopathic Granulomatous Mastitis (IGM) lesions before (left) and after (right) the steroid treatment.

However, we found no evidence of local trauma or autoimmune disease (1,14). These results indicate the lack of strong association between the smoking and oral contraceptive use and the disease.

The most common presentation of IGM is a rapidly growing breast mass, usually accompanied by inflammation (7). Abscess, chronic draining sinus formation, nipple retraction, and appearance of peau d'orange constitute other manifestations of the disease (17). In keeping with this evidence, 85% of our patients presented with breast mass, accompanied by abscess. The disease usually presents unilaterally with no predilection for any particular site, although there is a suggestion of propensity for extra-areola involvement (14,18), and we did observe an areola mass in 17% of our patients with IGM. Although upper outer quadrant was the most affected one, all the other regions of the breast were almost equally represented in our series.

Breast carcinoma is the most important differential diagnosis for IGM. In a number of studies, half of the patients with IGM in the preoperative setting have had suspected malignancy based on clinical and radiological signs (5,9). Radiology has limited value in the diagnostic work-up of patients with IGM (15,19,20), and thus pathologic diagnosis is crucial in the planning of treatment for these patients. Cytologic analysis by FNAB may identify IGM, but it is usually insufficient for definitive diagnosis and may be misleading (9). In a study by Kok et al. (7), IGM was diagnosed in four of 23 patients studied by FNAB. As mastectomies are frequently reported to have been performed unnecessarily on the basis of FNAB, histopathologic examination by means of trucut biopsy has a significant role in obtaining a definitive preoperative diagnosis (7,21). Familiarity with this rare entity is also important for the pathologic identification of IGM. We obtained preoperative diagnosis of IGM in 46 patients by means of trucut biopsy, with 100% accuracy. To our knowledge, this is the highest accuracy to be reported for diagnosis of IGM via trucut biopsy in a large patient sample.

The histologic features of IGM are noncaseating granulomas composed of epitheloid histiocytes, Langerhans giant cells, polymorphonuclear leukocytes, and neutrophilic micro abscesses, predominantly confined to the breast lobules (17). On the other hand, it is important to rule out infections such as tuberculous mastitis, *Corynebacterium*, actinomycosis, histoplasmosis, and noninfectious granulomatous conditions including sarcoidosis, Wegener's granulomatosis, and reactions to foreign bodies (1,11,14). Taylor et al. (11) reported that *Corynebacterium* leads to suppurative granulomas, and in some suspected cases, necessitates specific culture on medium containing 1% Tween 80 for confirmed diagnosis. Renshaw et al. (22) detected these lipophilic organisms within the vacuoles by Gram stain. Therefore, particular attention is required to identify these organisms in the differential diagnosis of IGM. Molecular techniques such as PCR and specific stains of the lesion such as Gram, Ziehl-Neelsen, and PAS, therefore, are also executed as well as tissue culture. Unless there is a super-infection, culture of the lesion is sterile in the case of IGM (7,17). True to this, we observed only eight positive culture results in our study.

The management of patients with IGM varies broadly from conservative approaches to mastectomy (1,9,13,20,21,23). Lai et al. (5) reported spontaneous resolution in four of eight cases of IGM with a mean interval of 14.5 months for complete resolution. Wide surgical excision is traditional and the most commonly performed surgical intervention (4,9). Although limited excision may be possible, complete excision of the breast mass or involved inflammatory tissue provides more satisfactory results in terms of preventing further complications and recurrence (1,15). Breast abscesses must initially be drained. The role of antibiotics in the treatment of IGM is of little value (7). Antimicrobial therapy should be administered in cases of positive culture results for the biopsy samples. In the case of abscess or sinus formation, 2 weeks empiric antibiotic treatment is also recommended (6). The use of corticosteroids for the treatment of IGM was first proposed by DeHertogh et al. (24) in 1980. However, the optimal dose and duration of steroid administration has not been established. In previous studies, patients have been given an initial dose of 60 mg of prednisolone per day, gradually reduced over 2–11 months (2,9,24). Recent studies show the efficacy of a lower dose of steroids over shorter periods for the treatment of IGM (1,3,14). We administered a standard dose of 16 mg prednisolone twice daily for 2 weeks, with gradual reduction over 6 weeks.

Due to the rarity of IGM, definitive treatment strategies have yet to be established. Either surgical excision or steroid therapy may be applied as a first-line therapy (7,9). The former provides rapid improvement of the disease and the latter avoids surgical scarring.

Steroid treatment has been advocated in recurrent cases or those complicated by the presence of an abscess or fistula (3,14). Steroid therapy may additionally be used in refractory cases following excision (4,16). It may also be useful for reducing the size of lesions preoperatively (18). In our patients who had small lesions and mild symptoms, patients' preferences played an important role in treatment choice, while patients with more extensive disease and severe symptoms were mainly offered steroid therapy. The elimination of other infectious disease is essential before the onset of steroid treatment. The adverse effects of steroids, such as glucose intolerance and cushingoid features, and the relative merits and disadvantages of treatment, should be individually assessed for each patient. Other immunosuppressive drugs such as methotrexate and azathioprine may also be used in patients with steroid resistance and in those with steroidal side effects (10).

Postexcision recurrence rates of 16–50% have been reported for IGM (7,15). Yau et al. (6) detected all disease recurrence within 6 months of surgical excision and recommended delayed breast reconstruction. Similarly, we detected all disease recurrence within 3–9 months of recovery. Kuba et al. (9) reviewed 248 patients with IGM; the rate of recurrence was 23.6% in 144 patients treated by excision and 25.8% in 31 patients treated with steroids. In all patients who had been treated with steroids, recurrent disease was cured by repeated therapy, and thus excellent outcomes were obtained without surgical intervention in 93.5% of the patients. In our study, the rate of recurrences for both treatment approaches were quite low (16.6% for local excision and 20% for steroid treatment) compared with the literature. However, these rates are still worrisome for surgeons and patients making the close follow-up mandatory. On the other hand, the successful treatment of all eight recurrent diseases in our study by switching to or combining the medical and surgical methods indicates that treatment can be improved by tailoring the management according to the clinical status of the patient.

In conclusion, breast mass with associated inflammatory signs in young patients is suggestive of granulomatous mastitis. It is essential to differentiate IGM from breast carcinoma. Due to the limited value of radiology, preoperative histopathologic confirmation by trucut biopsy is an important step in planning treatment for patients with IGM. Although there is no consensus on the optimal treatment, surgical excision or steroid therapy is applied as a first-line therapy. Treatment is designated according to disease dimension, severity of the symptoms, and the patient's health and treatment preferences. Because of its tendency to recur, close follow-up of patients with IGM is essential.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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