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CLINICAL TRIAL

Corticosteroid treatment and timing of surgery in idiopathic granulomatous mastitis confusing with breast carcinoma

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Abstract Idiopathic granulomatous mastitis (IGM) is an uncommon chronic inflammatory lesion of the breast with an uncertain optimal treatment regimen, the physical examination, and radiologic features of which may be confused with breast carcinoma. In this study, we aimed to describe the clinicopathologic characteristics of 33 patients who admitted to our breast policlinic and took the diagnosis of granulomatous (idiopathic and non-idiopathic) mastitis, and report the place of corticosteroids and the timing of surgery in the treatment of patients with IGM. The clinical features of 33 patients who presented to our breast policlinic with the complaint of breast mass and reached the final diagnosis of GM between March 2005 and October 2009 were reported. The most common symptoms were mass (*n*: 27) and pain (*n*: 11). Ultrasonography (USG) and biopsy were performed in all of the patients. Mammography (MMG) was performed in 9, and magnetic resonance imaging (MRI) in 10 patients. The diagnosis of idiopathic lobular granulomatous mastitis (ILGM) was made in 25 patients and tuberculous mastitis (non-idiopathic GM) in the remaining 8 patients. Twenty-four patients received steroid treatment except one who was pregnant. After giving birth, she also received steroids. One of the patients who developed recurrence after 11 months repeated the steroid therapy. Eight patients with tuberculous mastitis were placed on a regimen of antituberculosis therapy for 6 months. In the diagnosis of IGM, physical examination, USG, MMG, and even MRI alone may sometimes not be enough. They should be discussed altogether and the treatment should begin after definitive histopathologic result. Fine needle aspiration biopsy for cytology will result in a high level of diagnostic accuracy, however, core biopsy will reinforce the exact result. Corticosteroid therapy has been shown to be efficacious for IGM, but in the existence of complications such as abscess formation, fistulae, and persistent wound infection, surgical treatment has been the first method of choice.

Keywords Idiopathic · Granulomatous · Lobular · Mastitis · Corticosteroid

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Introduction

Idiopathic granulomatous mastitis (IGM), also known as idiopathic granulomatous lobular mastitis (IGLM), is a rare chronic inflammatory disease of the breast that may simulate the clinical and radiological characteristics of breast cancer [1–3]. Most of the patients are relatively young women under 50 years of age and pregnancy, lactation, and oral contraceptives may be the predisposing factors [1, 4]. It usually involves the unilateral breast and every quadrant region except for the subareolar area [4, 5]. IGM is characterized histologically by necrotising chronic granulomatous lobulitis and abscess formation [6, 7]. Clinical information and the description of radiographic features of IGM may help in the differentiation between IGM and breast cancer, however, histological confirmation is still required for the proper diagnosis and treatment of the lesion [3]. The treatment choices include corticosteroids, antibiotics, abscess drainage, wide surgical resection, and even mastectomy [8, 9]. However, the optimal treatment of patients is uncertain. In this study, our purpose was to report our clinical experience in 33 GM patients 25 of which were idiopathic and we believe that this is the largest series reported in the literature.

Materials and methods

Among 28,000 patients presenting to our breast policlinic between March 2005 and October 2009, 33 patients who had exact histopathological diagnosis were included in the study. The recorded initial clinical findings included palpable nontender mass in 19, tender mass in 8, and pain without a mass in 9 patients. Abscess formation (*n*: 14) and fistulae tract to the skin (*n*: 4) (Fig. 1) were detected. Axillary lymph nodes were palpable in one patient who had a 1-cm palpable breast mass. Every patient had ultrasonography (USG) examination (Fig. 2), however, in three patients the mass could not be visualized. Mammography (MMG) was performed in 9 (age > 35), and magnetic resonance imaging (MRI) was used in 10 patients for diagnosis. Three of the patients showed BIRADS 5 lesions in MMG. Tissue biopsies were done in 14 patients who had abscess drainage. All slides were examined with hematoxylin–eosin (H&E) and special stains such as Gram, Ziehl–Neelsen, and periodic acid-Schiff. Bacterial cultures, tuberculin (purified protein derivative (PPD)) skin tests were negative and chest radiographs were normal.

Fig. 1 View of the right breast in a IGLM patient with fistula formation

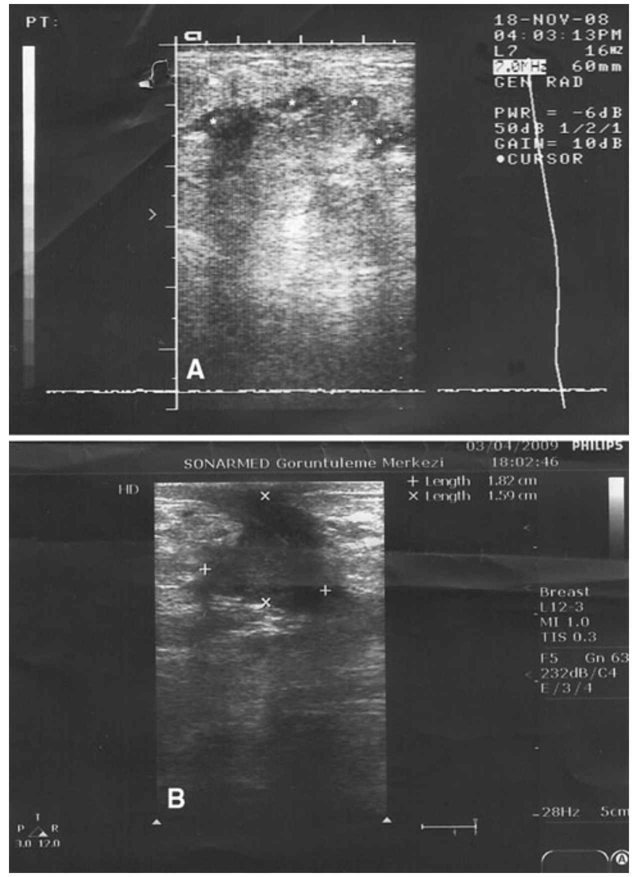

Fig. 2 **a** Sonographically an inhomogeneous, hypoechoic lesion composed of tubular echo-free structures (*). **b** Sonogram shows an irregular hypoechoic mass

Results

Clinical features

The mean age of affected women was 35.3 (range: 22–52) years. Most of the patients (*n*: 30) were of reproductive age. Three of the patients reported oral contraceptive use at the time of diagnosis. All of the patients except 1 had given birth to a mean number of 2.37 children and except 3, all breast-fed [mean 16.7 (range 1–30) months]. At the time of diagnosis, one of the patients was pregnant (for 8 months) and two of them were breast feeding.

Common presenting symptoms were mass in the breast (*n*: 27) and pain (*n*: 17). The masses were quite hard and measured clinically 1.3–9 cm (mean 3.6 cm) in size. In 14 patients, the overlying skin was inflamed. Nipple inversion was found in three patients. Axillary lymphadenopathy was established in 12 patients. Four patients presented with fistulae. The left breast was involved in 15 cases and the right was in 18. Synchronous or metachronous involvement of the contralateral breast was not found.

Radiologic evaluation

Mammographic examination showed ill-defined mass in all cases and an asymmetric density with no distinct margins in nine patients. Sonographic examination revealed an irregular hypoechoic mass in 14 patients, hypoechoic nodular structures in 9, and focally decreased parenchymal echogenicity with acoustic shadowing in 7 patients. USG was normal in three patients. MRI was performed in 10 patients and showed focal homogenous enhancing masses with irregular borders in 6 patients and parenchymal distortion in 4 patients. In 16 patients, the lesions were considered as malignant neoplasms according to the clinical and radiological findings before the biopsy results (Fig. 3).

Histopathologic evaluation

Ultrasonography guided fine needle aspiration biopsy (FNAB) and core biopsy were performed in all patients who had palpable mass. In eight patients, diagnosis of tuberculous mastitis was confirmed clinically and histopathologically. In nine patients, total excision of the mass was recommended since the malignancy could not be excluded. As a result, 25 patients who had non-caseating granulomatous inflammation were diagnosed with IGLM (Fig. 4). Histopathologic examination of the specimens showed scattered granuloma formations composed of epithelioid histiocytes and giant cells accompanied by lymphocytes, neutrophils, plasma cells, and eosinophils.

Treatment

Eight patients with tuberculous mastitis were placed on a regimen of antituberculosis therapy for 6 months.

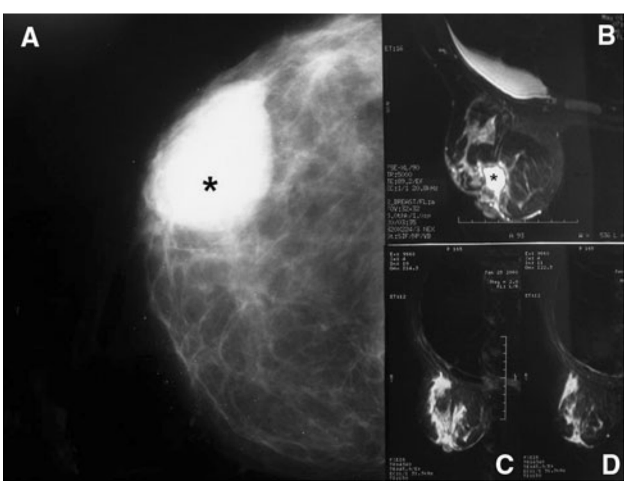

Fig. 3 **a** Craniocaudal mammogram of the right breast of a woman with IGLM. A focal asymmetric density (*). **b** Intensive homogeneous enhancement of the lesion (*) in MRI before treatment and **c**, **d** appearance after treatment

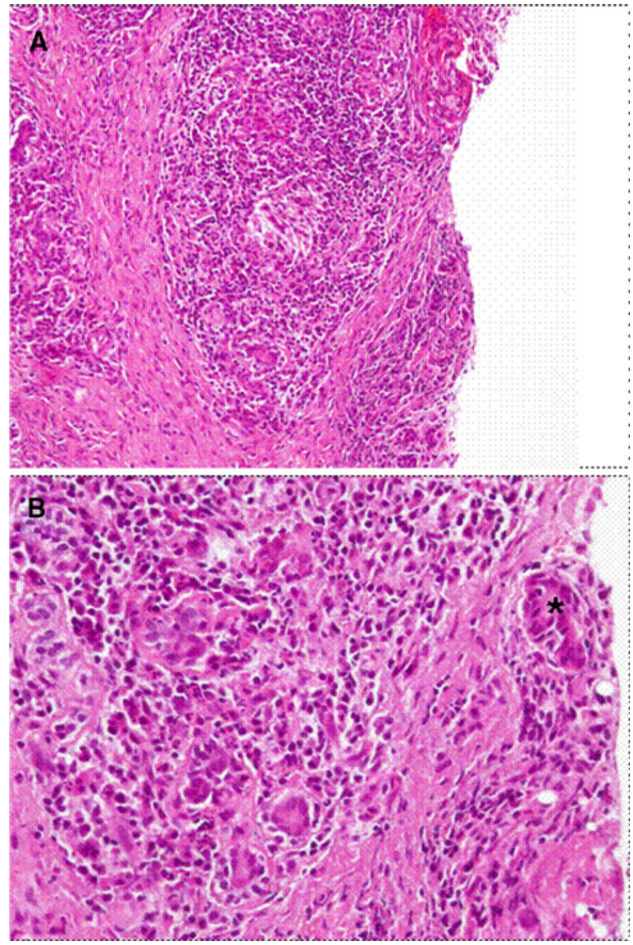

Fig. 4 Biopsy specimens demonstrating the **a** granulomatous inflammation (hematoxylin and eosin, ×10) and **b** a lobule with giant cells (*) (hematoxylin and eosin, ×40)

Twenty-five patients with IGM received steroid treatment after their initial treatment. In 14 patients who had abscess formation, surgical drainage was performed (2 patients were breast feeding and 1 was pregnant). Four patients who had fistulae tract to skin received steroid treatment after dermatologic consultation. In nine patients (two had abscess formation) who could not be differentiated from carcinoma, steroids were used after total excision of the lesions (Table 1). Standard treatment dose was 16 mg prednisolone twice a day for 2 weeks and thereafter the dose was slowly tapered and the therapy was stopped 2 months later. One of the patients who was over 70 kg used 24 mg prednisolone in the morning and 16 mg in the evening for 2 weeks according to the endocrinology consultation.

Follow-up

The median follow-up time was 7 months (range 1–48 months). The non-IGM patients treated successfully by

Table 1 Treatments used in patients with IGM

Patients (*n*)	Treatment modalities
14	Abscess formation → Surgical drainage → Steroid
4	Fistulae formation → Dermatology → Steroid
9	Total excision (carcinoma?) → IGM → Steroid

antituberculosis medication were followed by physical examination and USG in every 3 months. One of the patients left follow-up 6 months later because of moving to another city. Recurrence developed in one patient who had abscess drainage 11 months ago, and she was treated by repeated drainage and steroid therapy. Six patients receiving steroid treatment had complaint of gaining weight (3–8 kg). However, they returned to their normal weight after completing the therapy. One patient had a glucose level of 275 mg/dl, but it was regulated by diet.

Discussion

Granulomatous mastitis of the breast was first described as an entity in 1972 by Kessler and Wolloch [6]. Since then, case reports and small series mostly reviewing the clinical and pathologic findings of the disease have been reported [7]. This specific entity is separated from ductal ectasia and periductal mastitis, which are also associated with active granulomatous inflammation and, as a result of distinctive pathological features, the term granulomatous lobular mastitis was recommended by Going in 1987 as being more specific than the generic term of IGM or simply granulomatous mastitis [6, 8]. The granulomas were composed of epithelioid histiocytes, with occasional Langhans-type multinucleate giant cells, eosinophils, and scanty collections of polymorphonuclear leukocytes [10]. The absence of necrosis and a predominantly neutrophilic infiltrate in the background favor a diagnosis of GM [11].

It has been considered as rare, chronic, nonspecific granulomatous process, affecting the breast in relatively young patients, especially parous women as a tender, unilateral, firm, discrete extra-areolar breast lump in a lobular distribution, often associated with inflammation of the overlying skin [1, 9, 10].

The etiology of IGM remains unclear [1, 6]. The postulated causes have included autoimmune disease such as granulomatous thyroiditis, granulomatous prostatitis, granulomatous orchitis [1, 2, 12, 13], immune response to local trauma, local irritants [2], undetected organisms such as viruses, mycotic, and parasitic infections [1, 2, 12, 14], hyperprolactinemia, diabetes mellitus, alpha-1 antitrypsin [15] and the use of oral contraceptives [1, 6, 12, 16]. It is emphasized in relationship with pregnancy and lactation [2, 8, 12]. On the other hand, it is also reported that there appeared to be no association with breast-feeding, smoking, or any hormonal treatment [4, 17]. Imoto et al. [4] reported the period between the most recent delivery and the initial complaint of a tender breast mass from a few months to 8 years. In our study, all of our patients had the history of breast feeding.

Diagnosis of IGM should be one of exclusion of either other known causes of acute as well as chronic inflammatory and infective lesions of the breast including tuberculosis, brucellosis, filariasis, actinomycosis, sarcoidosis, histoplasmosis, Wegener's granulomatosis, and giant-cell arteritis or breast cancer, foreign-body reaction, duct ectasia (plasma cell mastitis, subareolar granuloma, and periductal mastitis), and fat necrosis [2, 3, 11, 12, 18]. Other possible causes of granulomatous inflammatory lesions of the breast can be excluded by serologic tests, histologic analysis by staining with either modified Ziehl–Neelsen, periodic acid-Schiff with diastase predigestion, or Gomori's methenamine silver stains, and by microbiologic workup of the effected tissue (fresh material from the surgical specimen) for aerobic and anaerobic bacteria, mycobacteria, and fungi [1, 3]. Serologic and bacterial tests are usually negative and no pathogenic microorganisms were detected in our series.

Idiopathic granulomatous mastitis is rare in older patients [18]. The mean age of our patients with granulomatous mastitis (35.3 years) was compatible with the literature. Unilateral involvement is usual with no predilection for any particular site, although it tends to spare the subareolar region [2]. In our study, the left and right breasts were involved in 15 and 18 cases, respectively. Almost a quarter of the patients have bilateral disease. Nipple retraction, abscess and sinus formation, and axillary lymphadenopathy up to 15% may be present [5]. These findings also suggest breast carcinoma and the initial clinical diagnosis is often carcinoma particularly in the older women, especially if draining lymph nodes are enlarged. Repeated aspiration cytology or excisional biopsy is recommended to avoid misdiagnosing granulomatous mastitis as carcinoma [4]. In the past, failure to obtain a histologic diagnosis has resulted in mastectomy, or radiotherapy, based on the clinical impression of carcinoma [1]. Therefore, the use of multiple assessments containing clinical and histologic examinations as well as imaging modalities are required for diagnostic accuracy [2].

Although it can mimic breast cancer clinically and radiologically, neither MMG nor USG is stated to play a significant role in the differential diagnosis of granulomatous mastitis [19]. USG has been reported to show findings specific for granulomatous mastitis in same cases, but all cases still require histopathologic confirmation for diagnosis, since both MMG and USG can be misleading [2, 15, 20]. Yilmaz et al. [5] stated that an asymmetric density on mammograms and a heterogeneous echo pattern with tubular hypoechoic structures on USG was suggestive of IGM. The role of MRI in the characterization of inflammatory processes of the breast is nonspecific, but MRI is useful in patients who have no significant pathology on MMG or US [2].

Generally granulomatous mastitis is a self limiting condition. As most patients are suspected of having a malignancy, most have undergone either an incisional or, if amenable, an excisional biopsy [8, 9, 21]. Due to the misleading findings, sometimes unnecessary mastectomies have been reported, therefore, it seems that the diagnosis of GM is a histologic diagnosis that cannot safely be made on cytologic grounds [2].

The optimal treatment of GM is still unclear. There is insufficient data about antibiotherapy use on GM. There is fairly high incidence of complications, such as abscess formation, fistulae, and chronic suppuration, the treatment of which require a through search for organisms in the initial specimen. Mixed aerobic and anaerobic infections may be seen and antibiotics should be used [2]. If no organisms are detected, steroid therapy has been found to be useful in some of these persistent cases [9, 22].

Complete resection of the affected tissue, with or without corticosteroid therapy has often been recommended as the optimal treatment, with long-term follow-up, as relapse in up to 38% of patients and delayed wound healing can occur [3, 4, 23, 24]. Surgical excision can be therapeutic as well as useful in providing exact diagnosis. After excision, if there is no delayed wound healing, infection or recurrence, no further therapy is needed [1, 2]. DeHertogh et al. [25] were the first to recommend the use of corticosteroids for the treatment of granulomatous mastitis. Steroid treatment can be administered after excision for complicated and resistant cases, or those patients who have had an incisional biopsy only and it may also be wise to give steroids to initially unresectable lesions before surgery [1, 2]. The weighing of possible risks and benefits of steroid therapy are difficult as a result of the small number of cases reported [1].

Steroid treatment decreases lesion dimension and augments complete healing after excision [2]. Early recognition and administration of steroid treatment might prevent repetitive, deforming breast biopsies. Satisfactory results have been reported with high doses of prednisone (60 mg/day for 2 weeks), but there has been reluctance for side effects, such as glucose intolerance and cushingoid features [1, 2]. Our standard treatment dose was 16 mg prednisolone twice a day for 2 weeks and thereafter the dose was slowly tapered and the therapy was stopped 2 months later. We had fairly satisfactory results with this dose and had only one recurrence 11 months after the first therapy.

The main concern in giving steroids to these patients is the possibility of having missed an infectious cause [1]. After a specific infectious cause is eliminated, steroid therapy has been found to be useful in some of these persistent cases [7, 13, 25]. It should not be forgotten that steroids exacerbate infectious disease of the breast, so exclusion of an infectious etiology with negative special stains, negative cultures and no evidence of systemic infection [e.g., normal chest X-ray film and negative PPD-tuberculin-skin test] is essential before the treatment [1]. Akcan et al. [2] suggested to use steroids only in recurrent and complicated patients. It is stated in the literature that in the cases resistant to the other therapies, immunosuppressive agents like methotrexate or azothioprin could also be used [19].

Conclusions

Granulomatous mastitis treatment is complicated and needs patience and long-term follow-up. The primary goal in these patients most of whom are young is to avoid confusion with carcinoma and not to miss malignancy. In specific infections, the treatment is specific to the disease, although in granulomatous lobulitis systemic steroid is proven to be useful. In the presence of abscess, drainage is the first choice of treatment, but in BIRADS 5 lesions, biopsy and complete excision should be done. In some cases, although the mass is palpable, radiologic studies may be negative.

Conflicts of interest statement None of the authors have any conflicts of interest.

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