Granulomatous Mastitis: Clinical, Pathological Features, and Management

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Abstract: This clinical study was conducted to present clinical, radiologic, and histopathologic features of Granulomatous Mastitis (GM) and evaluate the result of surgical and steroid treatment. Sixteen cases diagnosed histologically as GM were reviewed. Patient characteristics, clinical presentation, radiologic imaging, microbiologic, histopathologic assessment, treatment modalities, recurrence, morbidity, and follow-up data were analyzed. Majority of the patients were child bearing age and all of the patients had a history of breast feeding. Radiologic findings were nonspecific. Histopathology showed the characteristic distribution of granulomatous inflammation in all cases. In 12 cases, surgical excision of the lesion with negative margins was performed. Four cases required quadranectomy because of wideness of the disease. Three patients who had local reoccurrence and three resistant patients were treated by oral prednisone after surgical attempt. Complete remission was obtained and no further recurrence was observed in this patients. GM predominantly occurs in premenopausal women and the clinical symptoms might be misjudged as breast cancer. Histopathologic examination remains the gold standard for the diagnosis. Wide excision of the lesions is the recommended therapy and we suggest steroid therapy in resistant or recurrent disease following the idea that the disease has an autoimmune component.

Key Words: granulomatous mastitis, steroid, surgery, treatment

Granulomatous mastitis (GM) is a rare inflammatory breast disease with absence of an obvious etiology. Multiple etiologies such as tuberculosis (TB), sarcoidosis, foreign body reaction, and mycotic and parasitic infections have been suggested (1). Although it is a benign condition and usually presents with sinus formation and abscesses, clinical and radiologic features may mimic breast cancer (2). Not only mammographic features but also fine-needle aspiration cytology (FNAC) findings are sometimes interpreted as malignant (3). Surgical excision and steroid therapy are the most commonly used treatments (4,5). However, the most appropriate method that satisfies all requirements for the ideal treatment (quick healing, no hospital admission, minimum patient inconvenience, and low recurrence) still remains unclear. Moreover, treatment is associated with recurrent attacks. High rate of recurrence (16–50%) has been reported (6,7).

Although GM has been first described by Kessler and Wolloch in 1972, since then there have been a few studies evaluating etiology of GM and treatment modalities (8).

The aim of this study was to present clinical, radiologic and histopathologic features of GM and evaluate the result of surgical and steroid treatment.

MATERIALS AND METHODS

Between September 2003 and December 2007, 16 cases diagnosed histologically as GM, identified from surgical and pathologic records at the Department of Surgery, Mersin Medical Faculty, Mersin, Turkey, were reviewed retrospectively. The patients who had characteristic histopathologic features of a noncaseating...
granulomatous inflammation without any evidence of specific underlying causes included the study. Patient characteristics (including age, marital status, number of pregnancies, lactation, breast feeding duration, use of contraceptives, nicotine abuse, and presence of systemic disease and family history), clinical presentation, mammography (MM) and/or breast ultrasound (US), Magnetic resonance imaging (MRI), microbiologic and histopathologic assessment, treatment modalities, recurrence, morbidity, and follow-up data were analyzed.

Diagnosis of GM was confirmed histologically in all cases by core needle or open surgical biopsy. All slides were examined with hematoxylin–eosin (H&E) and special stains for tuberculosis and fungal infections. Microbial cultures (aerobic) were performed routinely in all patients. Lövenstein Jansen culture for tuberculosis and acid resistance bacteria controlling have been performed in all patients. Polymerase chain reaction (PCR) on paraffin-embedded tissues taken from the excision materials was performed and the diagnosis of TB mastitis was also analyzed.

All patients underwent a surgical excision of the lesion for inflammatory granulomatous tissue. They also administered antibiotic therapy in the postoperative period. Steroid therapy was used in six patients who had recurrence following wide excisional biopsy or resistant disease. Before initiation of steroid therapy, incision of the abscess combined with antibiotic therapy was applied. Steroid therapy with prednisolone 30 mg/day is administered for 8 weeks, and continued until complete remission.

### RESULTS

From September 2003 to December 2007, 234 patients were treated in our clinic for benign breast disease. Of these, 16 patients with GM were included in the study. These patients represented 6.8% of all patients with benign breast diseases who underwent surgery for benign breast disease in our clinic during the study period. Median patient age was 34 years (24–51 years). Fifteen patients were premenopausal and only one patient was postmenopausal. All of the patients had a marriage history. All of the patients had at least one pregnancy history. Two of them had a recent lactation history in 6 months. Fifteen of the patients had at least 12 months breast feeding history. Four patients had an oral contraceptive usage history (one current and three previously). Six patients had a history of nicotine abuse. Two patients were diabetic. Four patients had a tuberculosis history in their family. One had a breast malignity history in her mother and one had in her aunt. (Table 1 summarizes the characteristics of patients).

Clinical impression of breast abscess was presented in eight patients. Four patients revealed inflame skin and edema in affected breast. Four patients presented with fistula formation. All of the patients had unilateral disease. The right breast was affected in nine cases and the left breast was involved in seven cases. Eleven of the patients had GM in upper lateral quadrant. Three of them had lower lateral and two of them had upper medial quadrant. And four of the patients had palpable axillary lymphadenopathy.

| Table 1. Clinical Characteristics of Patients with GM |
|---|---|---|---|---|---|---|---|---|---|
| Age | Number of pregnancies | Menopause status | Lactation in 6 months | Breast feeding (months) | Oral contraceptive | Nicotine abuse | Systemic disease | Family history |
| 1 | 27 | 2 | Premenopause | + | 12 | – | + | – | – |
| 2 | 37 | 3 | Premenopause | – | 18 | – | – | Diabetic | Diabetic |
| 3 | 41 | 2 | Premenopause | – | 24 | – | + | – | Mother breast malignity |
| 4 | 36 | 1 | Premenopause | – | 18 | – | – | – | – |
| 5 | 24 | 2 | Premenopause | – | 12 | – | + | – | Uncle tbc |
| 6 | 51 | 3 | Postmenopause | – | 30 | – | – | – | – |
| 7 | 36 | 1 | Premenopause | – | 12 | – | – | – | Parent tbc |
| 8 | 35 | 1 | Premenopause | – | 9 | – | + | – | Parent tbc |
| 9 | 31 | 3 | Premenopause | – | 12 | – | – | – | – |
| 10 | 28 | 2 | Premenopause | + | 18 | – | – | – | – |
| 11 | 35 | 2 | Premenopause | – | 12 | – | + | – | Parent tbc |
| 12 | 27 | 2 | Premenopause | – | 12 | – | – | – | – |
| 13 | 31 | 3 | Premenopause | – | 24 | – | – | – | – |
| 14 | 26 | 2 | Premenopause | – | 12 | – | – | – | Aunt breast malignity |
| 15 | 37 | 1 | Premenopause | – | 36 | – | + | – | – |
| 16 | 42 | 4 | Premenopause | – | 18 | – | – | – | – |
Table 2. Diagnostic Modalities Applied in GM Patients

| Modality                | Patient | Findings                                                                 |
|-------------------------|---------|--------------------------------------------------------------------------|
| Ultrasonography         | 16      | Heterogeneously hypoechoic lobular lesion (six patients), abscesses formation (five patients), hypoechoic tubular structures (three patients), massive parenchymal heterogeneity (two patients) |
| Mammography             | 9       | Dense breast pattern (four patients), discrete opacities (two patients), spicular asymmetrical dense lesions (one patient), parenchymal distortion and asymmetry (two patients) |
| Magnetic resonance      | 4       | Heterogenous lesion with spicular borders (one patient), heterogeneous circumscribed lesion (one patient), heterogenous signal increase in parenchyme (two patients) |

Table 2 shows the results of the imaging procedures. US was performed in all cases. MM was performed for nine patients. Four of the cases were examined with MRI. Ultrasonographic examination showed heterogeneously hypoechoic irregular lobular lesion with posterior acoustic enhancement in six patients, abscesses formation in five patients, hypoechoic tubular structures in three patients and massive parenchymal heterogeneity in two patients.

Among nine patients who underwent MM, dense breast pattern without abnormal findings were observed in four cases, solitary or multiple discrete opacities were observed in two patients, focal asymmetrical dense lesions with spicular borders were observed in one patient and parenchymal distortion and asymmetry were observed in two patients.

Evidence of axillary lymph node enlargement was observed in three patients using MM and in two patients using US.

Magnetic resonance imaging finding in one patient was centrally hypointense, peripherally hyperintense, heterogeneous lesion with spicular borders that showed type I pattern. The other patient’s finding was a circumscribed lesion with heterogeneous contrast enhancement. Thickness under skin and heterogeneous signal increase in the parenchyme in T2A with type 1 pattern were findings in other two patients (Figs. 1 and 2).

Microbial cultures for aerobic microorganisms were performed routinely in all patients. In three cases, methicillin sensitive coagulase negative staphylococcus obtained in microbial cultures. Special stains for tuberculosis and fungal infections were negative. There was no evidence of tuberculosis in cultures. Polymerase chain reaction (PCR) was performed and tuberculous mastitis was not demonstrated in any patient.

Core needle biopsy was performed in 12 of the patients before surgical intervention. In nine of these cases, diagnosis of GM was confirmed histologically.

The aspirated materials showed evidence of granulomatous inflammation. Sixteen patients underwent an excisional biopsy and in each case the biopsy showed...
GM. Microscopically, all cases showed noncaseating granulomas involving the breast parenchyme. Langerhans-type multinucleated giant cells, histiocytes, eosinophils, and polymorphonuclear leukocytes were present in the granulomas along with lymphocytes and plasma cells. There is an absence of necrosis and a predominantly neutrophil infiltrate in the background (Fig. 3). Micro-abscess formation was observed in two patients. There was no evidence of tuberculosis or primary vasculitis.

In 12 cases, surgical excision of the lesion with negative margins for inflammatory granulomatous tissue was performed. Wideness of the excision decided for the margins of the disease. Therefore four cases required quadrantectomy because of wideness of the disease. In nine of the cases, GM was confirmed using tru-cut biopsy preoperatively. In seven cases, GM was confirmed after drainage of abscess and wide excision was performed for these cases at the second operation.

The median follow-up was 24 months (range 6–36 months). During this period, in 12 cases surgical attempt was performed more than one time. In seven of these cases, second operation was performed because GM was confirmed after abscess drainage as mentioned above. Three of the patients developed abscess formation at another area of the breast and three of them had local recurrence at the main disease place. Re-excision was performed for the local recurrence and wide excision for the recently developing abscess. Three patients who had local reoccurrence and three resistant patients were treated by oral prednisone after surgical attempt. Steroid therapy with prednisolone 30 mg/day was administered for 8 weeks. Complete remission was obtained based on clinical examination and the findings of US. And no further recurrence was observed in these patients. Any side effect of prednisone had not been developed in patients except striaes. Management of patients and follow-up data were given in Table 3.

**DISCUSSION**

Granulomatous Mastitis is an uncommon benign breast disease and its clinical symptoms might be misjudged as breast cancer (9). Idiopathic granulomatous mastitis and specific granulomatous mastitis are the two defined forms of GM. GM occurs usually in women of child bearing age (1,10). Decennium at diagnosis is generally in 3rd to 4th. The age of youngest patient ever reported was 11 years (11). GM occasionally has been reported in elderly patients. The oldest patient with GM reported in the literature was 83 years old (12). Similarly in our study mean age of the patients was 34 years. The youngest patient was 24 and the oldest one was 51 years old.

Studies have shown that GM has association with recent pregnancy and lactation (13). In our series, two of the patients had a recent pregnancy and lactation history. However, all of the patients had at least one pregnancy history. It has been reported that prolonged breast-feeding might result in long-term distension of acini and ducts; this may facilitate rupture of these structures inducing granulomatous response (14). We observed that majority of our patients had a breast feeding history of more than 12 months.
Granulomatous mastitis has also been reported to occur in some patients who received oral contraceptives (15). In our study, only one patient had a current history of oral contraceptive use, whereas three patients had previously used contraceptive pills. All patients except one were in premenopausal period.

The pathogenesis and etiology of GM is not clear. A correlation between many agents, such as local irritants, viruses, mycotic and parasitic infections, hyperprolactinemia, diabetes mellitus, smoking, and alfa-1 antitrypsin deficiency have been discussed but have never been clearly demonstrated (16–19). In our study, six patients had nicotine abuse and two of the patients were diabetic.

Specific bacteria cannot be detected in GM. Serologic and bacterial tests are usually negative. An underlying autoimmune process is often claimed as an etiology (20). Damage to the ductal epithelium produced by any of etiological factors could permit luminal secretion to leak into the lobular connective tissue, thereby the autoimmune reactions to this extravasated secretions from lobules have been hypothesized (3,11). However, systemic immune abnormalities have not been reported yet. In addition, GM has been associated with autoimmune diseases, e.g., erythema nodosum, lymphocytic alveolitis corresponding with sarcoidosis, Wegener granulomatosis, giant cell arteritis, or polyartheritis nodosa (21–23).

Recently, it has been pointed out that many reports come from developing countries such as Mediterranean countries (Turkey and Jordan) and Asia (Arabia, China and Malaysia) (5,11,12,24,25). No ethnic predisposition has been documented in GM, so this prevalence might be the reflection of underdiagnosis of tuberculosis mastitis. Sometimes routine histology studies are not sufficient to rule out the diagnosis of TB mastitis and PCR testing may be more useful. Interestingly in our study four of the patients had a tuberculosis history in their near family. However, we used PCR testing in all of our patients but in none of them TB has been found.

A breast mass is the most common clinic finding in GM. The penetration of the mass to the breast skin or the pectoralis muscle, nipple retraction, ulcerations of the skin, sinus formation, and axillary lymphadenopathy can be in the presentation of GM and these findings may suggest breast carcinoma (5,11). Therefore, there are cases reported about patients treated by mastectomy because of misdiagnosis. In our clinic although breast cancer was suspected in four patients because of the clinical manifestation of GM, all of the patients diagnosed as GM histopathologically and none of the patient required mastectomy for a misjudged diagnosis.

All of our patients had unilateral involvement. In the literature, the involvement is usually unilateral, whereas bilateral involvement has rarely been reported (16). GM can occur in both right and left breasts. In our study, there was no predominance in neither right nor left breast. Nine patients had the disease in right breast and seven had in left breast. In addition, GM can affect any quadrant of the breast, in our study majority of the patients had GM in upper lateral quadrant.

Most of the GM patients are young women therefore frequently MM findings were nonspecific in most of the patients. Radiologic findings of GM such as the presence of a focal asymmetrical density on mammography can mimic malignancy and differentiation GM from malignancy by MM is difficult (26). US may better characterize such lesions. Inhomogeneous hypoechogenicity with internal hypoechoic tubular lesions might suggest the possibility of GM. In our study, US was used in all patients with GM. In most of our patient, the sonographic appearance detected abscess formation. Recently MRI has been used in some studies and detected focal homogeneous enhancing masses with irregular borders (27). MRI is a complementary diagnostic modality in breast imaging and it can evaluate extent and reduction of the gm lesions. In our study, MRI findings were centrally hypointense, peripherally hyperintense, heterogeneous lesion and a circumscribed lesion with heterogeneous contrast enhancement. The patient with the finding of heterogeneous lesion with spicular borders showed type 1 enhancement pattern. According to the literature, the role of MRI in the characterization of inflammatory processes of the breast is nonspecific, but MRI can be useful in patients who have no significant pathology on MMG or US. In the patients with pathologic findings on MMG or US, MRI can be useful by its ability to demonstrate morphologic features of breast masses (4,7,27).

As the misleading clinical and imaging findings caught unnecessary mastectomies that have been reported in the literature, histopathologic evaluation plays a very important role in the diagnosis of GM. Diagnosis of GM can be made by FNAB or excisional biopsy. However, cytology may not always distinguish from those of carcinoma and other granulomatous
disease of the breast, such as specific infections (mycobacterium tuberculosis, fungus, and parasites), ductectasia, periductal mastitis, plasma-cell mastitis, sarcoidosis, and vasculitis (9,28). Therefore, histologic diagnosis of GM cannot safely be made on cytologic grounds alone (29). Adequate evaluation of a wide breast tissue sample examination may be needed for differential diagnosis of GM from other pathologies.

In our study, core needle biopsy which was performed before surgery successfully confirmed GM in nine of the 12 patients. Furthermore, in all of our cases the diagnosis of GM had been confirmed by surgical excision. Demonstration of granulomatous inflammation of the lobular units is required for a definitive diagnosis of GM (16,29). It presents a chronic non-caseating granulomatous inflammation and the infiltrate is composed of histiocytes, a few polymorphonuclear leukocytes, and multinucleated giant cells of the foreign body and Langerhans type (16,30). Abscess formation can occur. The possibilities of breast TB and sarcoidosis was considered in differential diagnosis. TB mastitis presents with caseating granulomas and acid-fast bacilli, whereas GM has discrete non-caseating granulomas. None of our cases showed TB mastitis histopathological features. In sarcoidosis, granulomas are diffusely present and by the characteristic lobular distribution distinguish GM from sarcoidosis (6). In addition, duct ectasia/periductal mastitis can mimic GM clinically and histologically. Ductal dilatation is a finding of duct ectasia/periductal mastitis and, in our cases no ductal dilatation has been shown.

In management of GM, frequently wide excision of the mass was performed (13,16,31). To decrease recurrence rate, negative surgical margins in terms of inflammatory tissue must be achieved. Surgical excision can be not only therapeutic but also useful in providing right diagnosis. Surgical excision including wide excision, quadrenectomy, and drainage of abscesses was performed in our cases. In two of our cases with fistula formation, methylene blue dye injected from the fistula and surgical excision was performed with negative surgical margins. In the literature, it has been shown that limited excision alone is of little benefit therefore wide local excision is the most common method of treatment. As it allows wide excisions or quadrantectomy, general anesthesia was preferred in all of our cases.

There are insufficient data about antiotherapy use on GM (31). GM is sometimes complicated by abscess formation, fistulae, or chronic suppuration. Mixed aerobic and anaerobic infections may be observed. Antibiotics had been used in all of our cases postoperatively.

However, the optimal treatment of granulomatous mastitis is still controversial. Steroid treatment is a choice of treatment as an conservative management (31,33,34). Satisfactory results have been reported with high doses of prednisone. Steroids have been used either after excision or before surgery. For complicated and resistant cases, steroids should be administered after excision. Steroid treatment decreases the mass dimension and may be used in unresectable lesions before surgery. In six of our cases, we administered steroid therapy after surgery. Steroid therapy with prednisolone 2–30 mg/day is recommended for at least 6 weeks (24). Some reports suggest that high doses of corticosteroids should be continued until complete resolution (10). Our patients who had been administered steroid therapy continued therapy for 8 weeks. In agreement with some reports that suggested the use of steroids in recurrent cases, we administered steroid therapy in recurrent cases or resistant cases. In some studies, the recurrence rate in surgical treatment is reported to be higher than that in steroid treatment. In our study with initiation of steroid treatment we controlled the disease process and prevented multiple deforming breast operations. And none of these patients had been showed recurrence after steroid therapy.

Steroids may exacerbate infectious disease of the breast, therefore in all of our cases exclusion of an infectious etiology was essentially performed before the treatment. Furthermore, the side effects of steroid therapy include glucose intolerance and cushingoid features. None of our patients who received steroid therapy showed side effects. In only one patient, striae have been found.

Major complications of GM are recurrences and fistula formation. In the literature, different recurrence rates (range, 16–50%) are reported after excision (6,7). In this study, recurrence developed in five (31%) patients. Excision of the recurrence and additional steroid therapy may be necessary. Three of patients with recurrence in our series were successfully treated by steroid therapy.

The process of the disease is characterized by slow resolution, long-term follow-up is often necessary (15). However, how long these patients need to be followed is not certain. The median period of follow-up was 24 months in our study.
CONCLUSIONS

Granulomatous mastitis is a rare disease with unclear etiology. GM predominantly occurs in premenopausal women and the clinical symptoms have often been misjudged as breast cancer. Since radiologically there is no characteristic appearance, histopathologic examination remains the gold standard for confirmation of the diagnosis. Wide excision of the lesions with negative margin under general anesthesia is the recommended therapy and we suggest steroid therapy in resistant or recurrent disease following the idea that the disease has an autoimmune component.

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