

Granulomatous Lobular Mastitis

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ABSTRACT: **Background:** Granulomatous lobular mastitis (GLM) is a rare disorder that can clinically mimic breast carcinoma. The recommendation for diagnosis and treatment of GLM has not yet been established.

Objectives: To assess a series of GLM patients, including their clinical presentation, diagnosis, treatment and outcome.

Methods: We retrospectively analyzed the clinical data and treatment of 17 female patients with biopsy-proven GLM. Breast tissue was obtained by a core needle biopsy (15 patients) or open biopsy (2 patients). Images were reviewed by an experienced radiologist.

Results: The mean age of the patients at diagnosis was 44.6 ± 12.6 years. Five patients (29%) presented with bilateral disease, and seven (41%) presented with a mass, suggesting the initial diagnosis of breast carcinoma. Treatment comprised observation alone (23%), antibiotics (58.8%) and/or corticosteroids (with or without methotrexate) (35%). At the end of the study 70.6% of the patients demonstrated complete remission. None of the patients developed any systemic (granulomatous) disease or breast carcinoma during the follow-up period (4.7 ± 3.8 years).

Conclusions: Core needle biopsy is mandatory for the diagnosis of GLM and the exclusion of breast carcinoma. The recommended treatment modalities are observation alone or corticosteroids; surgery should be avoided. GLM is a benign disease with a high rate of resolution and complete remission.

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KEY WORDS: granulomatous mastitis, inflammatory breast disease, breast carcinoma

Granulomatous lobular mastitis (GLM) is a rare inflammatory disorder of the breast first described by Kessler and Wolloch in 1972 [1]. It is a chronic non-necrotizing granulomatous inflammation around the lobules of the breast tissue without evidence of malignancy or necrosis [2]. Clinically, GLM may mimic mastitis, breast abscess or breast carcinoma

[3]. Effective diagnostic and management protocols for GLM have not yet been established. Prior to 1980, surgical excision of the lesion was routinely performed [4]. In recent years, corticosteroid treatment has been the mainstay of therapy [5]. We report here a single-center case series of 17 patients with GLM, including the diagnostic modalities (imaging and histopathology), treatment and clinical course.

PATIENTS AND METHODS

The Institutional Review Board approved analysis of the patients' data. Patients were retrospectively identified from both electronic database and hard-copy medical records. All images (ultrasound, mammography) were reviewed by an experienced radiologist. Demographic, clinical and laboratory data were obtained from the medical records. Patients were followed at the breast and/or immunology clinics (usually every 1–3 months), and the outcome of the patients was determined at their last visit. Evaluation for systemic granulomatous disease included chest radiograph and "routine" laboratory evaluation: complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), electrolytes, and liver and renal functional tests in all patients. In some patients, angiotensin-converting enzyme (ACE) and perinuclear/cytoplasmic anti-neutrophil cytoplasmic antibodies (p/c-ANCA) were also measured.

The pathology examination of the breast biopsies was processed as usual. The tissue was fixed in 4% buffered formalin for 6 to 24 hours and the paraffin blocks were cut to 4 μ m thick slices. For each case, eight slides cut at levels of 20 μ m were prepared; four of them were stained with hematoxylin-eosin (HE) for light microscopy examination. For the remaining slides periodic acid-Schiff (PAS) and Ziehl-Neelsen staining were used.

Complete remission was defined as the absence of breast mass or signs of breast inflammation without any medical treatment. Patients in whom the breast mass did not resolve completely or who needed medical treatment were considered as having partial remission. If there was no change in the breast mass or inflammation signs at the last clinical visit, the patient was defined as a non-responder.

Data are presented as mean \pm standard deviation (SD). Mann-Whitney test, Student's *t*-test and chi-square tests were

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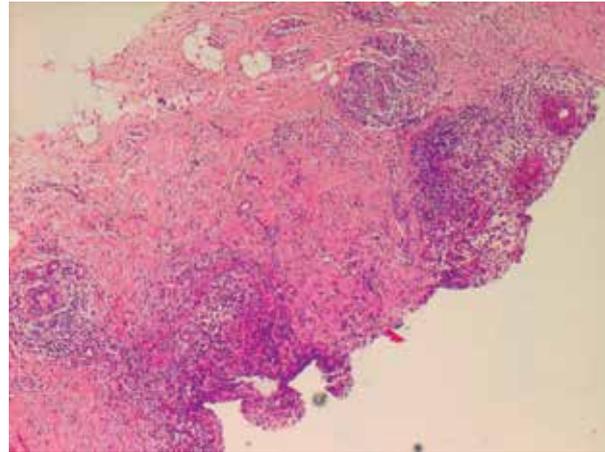
used for statistical analysis. $P \leq 0.05$ was considered statistically significant.

RESULTS

Seventeen female patients with GLM were identified between January 1999 and September 2012. Patients' demographic data, treatment and outcome are shown in Table 1. The mean age of the patients at diagnosis was 44.7 ± 12.6 (range 31–66) years. Seven cases (41.1%) presented with a breast mass suggesting the diagnosis of carcinoma, eight (47%) were initially diagnosed with mastitis, and the other two presented as breast abscess. Bilateral disease was evident in 5 cases (29%). One patient was diagnosed during the second trimester of pregnancy (patient 6). Eight cases (47%) showed an ultrasonographic mass whereas a mass effect was seen on mammography in only 3 (17.6%) of the patients without correlation between those two imaging modalities [Table 1]. Core needle biopsy was performed in 15 patients and an open biopsy in the other 2.

Pathology examination revealed chronic inflammation mainly around lobules, with multinucleated giant cells and epithelioid histiocytes forming a non-necrotizing granuloma [Figure 1]. In some cases, an admixed acute inflammatory

Figure 1. Breast tissue showing chronic inflammation with perilobular pattern and granuloma formation (HE x4)



infiltrate, ductal and periductal, was present [Figure 2]. PAS and Ziehl-Neelsen stains were negative in all cases.

Routine laboratory studies were normal in all patients (patient # 6 who was pregnant did not undergo chest X-ray) except for ESR/CRP which were elevated in six patients, four of whom (66.7%) presented as mastitis and only one

Table 1. Demographics, clinical presentation, imaging, treatment modalities and outcome in 17 patients with granulomatous lobular mastitis

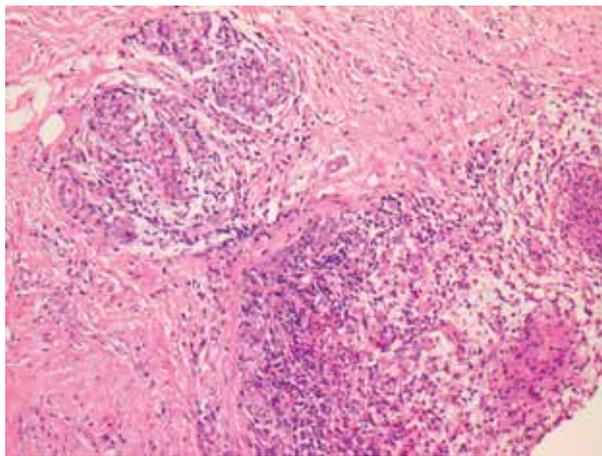
Patient #	Age at diagnosis (years)	Initial diagnosis	Unilateral/ Bilateral	Ultrasound	Mammography	Initial treatment	Rate of breast finding resolution (months)	Follow-up (years)	Outcome
1	32	Carcinoma	Unilateral	Normal	Mass	Excision	0.5	11	CR
2	44	Carcinoma	Unilateral	Mass	Increased density	Observation	Not resolved	13	PR
3	36	Mastitis	Unilateral	Mass	Not done	ATB*	0.5	7	CR
4	48	Abscess	Bilateral	Mass	Enlarged LN	ATB + drainage	1	6	CR
5	66	Carcinoma	Unilateral	Not done	Not done	Observation	Unknown	4	CR
6	30	Mastitis	Unilateral	Normal	Not done	Steroids	6	3	CR
7	37	Mastitis	Bilateral	Mass	Normal	Steroids + MTX	Not resolved	3	PR
8	53	Mastitis	Unilateral	Not done	Normal	ATB + drainage	Unknown	2	
9	50	Carcinoma	Unilateral	Not done	Increased density	ATB	3	2	CR
10	40	Abscess	Unilateral	Cysts	Mass	ATB + drainage	18	1.5	CR
11	72	Carcinoma	Unilateral	Mass	Mass	Observation	Unknown	1	CR
12	35	Mastitis	Unilateral	Cysts	Not done	ATB + drainage	Unknown	12	CR
13	66	Carcinoma	Unilateral	Normal	Not done	Observation	12	3	CR
14	45	Mastitis	Bilateral	Cysts	Increased density	ATB + drainage + steroids	24	4	CR
15	41	Mastitis	Bilateral	Mass	Normal	ATB + drainage + steroids + MTX	Not resolved	4	PR
16	34	Mastitis	Bilateral	Mass	Thick skin	ATB + drainage + steroids	Not resolved	3	PR
17	31	Carcinoma	Unilateral	Mass	Not done	ATB + drainage + steroids	Not resolved	0.5	PR

CR = complete remission

PR = partial remission. Patients 6, 15, 16 and 17 were on medical treatment at the last clinical visit. Patient 2 had a breast mass without medical treatment

ATB = antibiotic treatment: ciprofloxacin or amoxicillin/clavulanate, MTX = methotrexate (10-15 mg/week)

Figure 2. Perilobular chronic inflammation with granuloma formation with few neutrophils in the center of the lesion (HE x20)



(16.6%) as breast abscess. ACE was measured in five patients and was found to be mildly elevated (87 U/L, normal range 22–68 U/L) in only one patient (# 16). Following corticosteroid treatment, ACE levels returned to normal range. p/c-ANCA were determined in five patients and were negative in all five. None of the patients including the one who presented with high ACE levels revealed any symptoms or signs of systemic disease (e.g., sarcoidosis, tuberculosis or systemic vasculitis).

The initial treatment included observation alone (without any medical or surgical intervention) in four patients (all presenting with breast mass) and surgical excision in one. Antibiotic agents (ciprofloxacin or amoxicillin/clavulanate) were given to 10 patients (58.8%), either alone (2 patients), with drainage (4 patients) or with drainage and corticosteroids (4 patients). Corticosteroids (at a dosage of 30–40 mg/day of prednisone, orally) was the only treatment in one patient. Four other patients were treated with corticosteroids in addition to drainage and antibiotic treatment. Methotrexate (MTX, 10–15 mg weekly, orally) was added in two patients in whom the breast mass did not resolve despite steroid treatment (patients # 7 and 15).

The breast mass/mastitis completely resolved in 12 (70.6%) of our patients. In four of them the exact time of resolution is not known (defined as unknown in Table 1), but a later follow-up revealed complete resolution of the breast finding. In the other eight patients, resolution occurred 8.1 ± 8 months (range 0.5–24) following GLM diagnosis. Five patients were defined as partial remission: patient # 2 still had a breast mass at the end of the study period (after a follow-up of 13 years) without any need for medical treatment; in patients # 7, 15, 16 and 17 the disease course was chronic and they were on medical treatment (corticosteroids with or without methotrexate) at the end of the study period.

DISCUSSION

The main finding of our retrospective study is that GLM is a benign disease resolving completely in 70.5% of the patients within 8.1 ± 8 months from diagnosis. Moreover, at the end of the study period (mean follow-up 4.7 ± 3.8 years) none of the patients had developed breast carcinoma or any systemic disease such as sarcoidosis, granulomatosis with polyangiitis, or tuberculosis.

GLM is a rare disorder typically affecting women of child-bearing age [2], although in our series the mean age at diagnosis was quite high (44.7 ± 12.6 years). Nevertheless, GLM has been reported in children as well as in the elderly [6]. There is almost always a history of oral contraceptive usage, and it may develop (as in one of our patients) during pregnancy or lactation [7]. Although the pathogenesis of GLM is unknown, association with autoimmune disorders, oral contraceptive use, hyperprolactinemia [8], α -1-antitrypsin deficiency [8] or infection with *Corynebacterium kroppenstedii* [7,9] has been reported.

While bilateral disease has been reported previously [4], the rate in our study (29%) was quite high. GLM usually presents as a mass located in any area of the breast with the exception of the subareolar region [8]. The mass may be associated with pain, skin edema and reddening (including peau d'orange), nipple retraction, sinus track formation, frank ulceration, or axillary lymphadenopathy [10], suggesting a diagnosis of either breast carcinoma or inflammatory (infectious) breast disorder. Indeed, the initial clinical diagnosis in our patients was carcinoma in 7 (41%) and inflammatory breast disease in the other 10 (59%) [Table 1].

The differential diagnosis includes breast cancer, which can be excluded only by histologic examination, and bacterial infectious disease that is usually responsive to antibiotic treatment. Other diseases to be considered are tuberculosis especially in endemic areas, mycotic infection, systemic illness such as sarcoidosis and systemic lupus erythematosus (SLE), and foreign body reaction.

Mammography in GLM is often non-specific, with multiple discrete masses or areas of sizable unilateral focal asymmetry with indistinct margins suggesting the diagnosis of carcinoma [11,12]. More rarely, the mass is lobulated or there is a diffuse increase in breast density (as demonstrated in three of our patients) although this is dependent upon the inherent density pattern of the adjacent normal breast parenchyma. The sonographic features vary. The most common finding is an irregular hypoechoic mass with central radiation finger-like projections of tubular structures leading away from the mass [13]. Less commonly, parenchymal distortion with acoustic shadowing mimicking a carcinoma but without a discrete mass lesion may be seen. Thus, as demonstrated in our case series [Table 1], both imaging techniques have limited value in the diagnosis of GLM.

Although fine needle aspirate cytology may differentiate GLM from carcinoma, it is less accurate than core needle biopsy [14]. Thus, in agreement with previous studies [14], we recommend core needle biopsy (which was performed in 15 of our patients) for the diagnosis of GLM. In the vast majority of patients there is no indication or any advantage for the open biopsy procedure [3].

The characteristic histological features of GLM are non-caseating granulomata with epithelioid histiocytes, multinucleate giant cells and inflammatory infiltrate (predominantly neutrophils) with frequent microabscess formation and fat necrosis [15] [Figures 1 and 2]. In ductal breast carcinoma there are cords and nests of tumor cells with varying amounts of gland formation. The malignant cells induce a fibrous response as they infiltrate the breast parenchyma. In endemic areas, tuberculous mastitis tends to occur in younger women, with larger lesions, more fibrosis and eosinophilia, but fewer plasma cell infiltrates [15]. In sarcoidosis, a “naked” granulomata without an attendant lymphocytic infiltrate may be seen. The ruptured cysts demonstrate non-lobular inflammation and the ductal ectasia is associated with periductal fibrosis. Granulomatosis with polyangiitis has coincident vasculitis, and carcinoma shows specific cytokeratin expression on immunohistochemistry [15].

It should be noted that granulomatous disease of the breast may be a part of systemic disease such as sarcoidosis [16] or systemic vasculitis (e.g., granulomatosis with polyangiitis, Sjogren's syndrome [17] or SLE), although it is quite uncommon (< 1%). The breast clinical manifestations and imaging in such cases usually mimic breast carcinoma [17]. In the vast majority of cases other organs (lung in sarcoidosis, lung/kidney in systemic vasculitis) are involved prior to or concomitantly with the breast involvement. Breast involvement as the first manifestation of the above systemic disorders is extremely rare. Therefore, we recommend a complete medical history and physical examination with routine laboratory evaluation (CBC, ESR, CRP, electrolytes, liver and renal functional tests) in all GLM patients. Further specific imaging (e.g., chest computed tomography) or laboratory tests (ACE, p/c-ANCA) should be undertaken only in patients in whom systemic disorders are clinically suspected. Indeed, during a mean follow-up of 4.7 ± 3.8 years, none of our patients developed any systemic disorder.

The optimal management of GLM is not yet defined. In some patients (e.g., four of our patients) [Table 1], observational management alone is acceptable since spontaneous resolution without any treatment was reported in half the GLM patients within 15 months [18]. In agreement, 75% of our patients who did not receive any treatment revealed complete remission. Although there is no clear evidence for the efficacy of antibiotic treatment in patients with GLM without a proven secondary infection, several studies reported its usage in GLM patients [19]. Similarly, in our series 10

patients (58%) received antibiotic treatment either alone or in combination with other treatments [Table 1].

Primary surgical intervention by excision should be avoided since it may cause complications such as chronic sinus formation, poor wound healing and cosmetic disfigurement. Moreover, a high rate of recurrence has been reported following primary surgical treatment of GLM [20]. Thus, surgery should be reserved for patients who did not respond to medical treatment (mainly to corticosteroids) or for recurrence after corticosteroid discontinuation. Recently, percutaneous drainage, under sonographic guidance, was suggested [21]. In our series only one patient (# 1) underwent excision of the breast mass, since despite the negative (non-malignant) core needle biopsy, there was a high clinical suspicion of breast carcinoma that was eventually not found in the mass.

Corticosteroids (starting at a daily dose of 0.5–1 mg/kg prednisone) appear to be effective treatment for GLM [22]. In some patients, immunosuppressive agents such as methotrexate or azathioprine are needed either as steroid-sparing agents or in relapse following corticosteroid discontinuation [23,24]. In our series corticosteroids were used in six patients either alone (in one patient) or with other therapeutic modalities [Table 1]. Corticosteroids were given to patients who did not improve after the observation period or antibiotic treatment or drainage. Complete remission was observed in only two of our corticosteroid-treated patients (33%), probably because of a more severe disease. Due to the retrospective nature of our study, the real efficacy of corticosteroids treatment cannot be fully appreciated.

The overall outcome of our patients (mean follow-up of 4.7 ± 3.8 years) was quite good: 70.5% of the patients revealed complete remission which was defined as resolution of breast mass with the absence of any treatment. In contrast to previous reports [25], we did not observe any disease recurrence in patients who achieved complete remission. This may be due to the relatively short follow-up period in our study especially in the steroid-treated patients. The high rate of complete remission was not related to the initial clinical presentation (71% and 70% for patients presenting as suspected carcinoma or as mastitis/abscess, respectively). Complete remission was insignificantly higher among patients with unilateral disease (70.8%) as compared to those with bilateral disease (40%, $P = 0.1$). Due to the retrospective nature of our study we cannot assess the exact efficacy of the various treatment modalities. The fact that corticosteroids were given to patients with more severe disease, and the shorter follow-up of steroid-treated patients (2.9 ± 1.23 years) compared to the other patients (5.6 ± 4.4) may explain the less successful outcome of corticosteroid treatment.

To conclude, GLM is a rare disorder that can mimic breast carcinoma. Core needle biopsy is the recommended method for diagnosis and is mandatory in all cases in order to exclude breast carcinoma. Surgery should be avoided in GLM patients

unless all other treatment modalities have failed. The therapeutic approach includes observation alone or corticosteroids treatment in severe cases.

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