Granulomatous Lobular Mastitis: Antituberculous Treatment and Outcome in 22 Patients

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Keywords

Granulomatous lobular mastitis · Clinical presentation · Management · Antituberculous therapy

Summary

Background: Granulomatous lobular mastitis (GLM) is a rare chronic inflammatory condition of the breast. The purpose of this study was to describe antituberculous treatment of GLM and the long-term follow-up outcome.

Methods: This retrospective study included 22 patients who had been histopathologically diagnosed with GLM at the Second Hospital of Shandong University from January 2011 to March 2015. Clinical characteristics, ultrasonography and mammography findings, laboratory tests, treatment regimens, follow-up information, and recurrences were recorded. **Results:** All patients were female with a median age of 29 (range 23–44) years. The most common symptom was a breast mass with or without pain. Large irregular hypoechoic masses could be found in the breast ultrasounds of 13 patients. All patients received triple antituberculous therapy. During a median follow-up period of 40 months, 3 patients were lost to follow-up; of the remaining 19 patients, 18 achieved clinical complete remission and no recurrences were observed. **Conclusion:** GLM is an unusual benign breast condition that mimics breast carcinoma in its clinical and imaging presentation. Antituberculous therapy seems to be an effective alternative option in the treatment of GLM.

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Introduction

Granulomatous lobular mastitis (GLM), as a rare chronic benign inflammatory disorder of the breast, was first defined by Kessler and Wolloch in 1972 [1]. It usually affects women of child-bearing age, with the average age being 35 years [2]. Patients with GLM have a great diversity of symptoms but most commonly present with a breast mass with or without pain and sometimes skin ulcerations and sinus or fistula formation [3]. The etiology of GLM is still unknown. Several factors have been reported to be related, including microbiologic agents, hormonal effects, and immunologic disorder [4].

There is currently no consensus as to the ideal first-line treatment regimen. The main treatment approaches include antibiotics with repeated drainage, wide surgical excision or mastectomy, oral steroids, immunosuppression with methotrexate, and close follow-up [5]. The recurrence rate remains high even after mastectomy; therefore, nonsurgical management including steroids, methotrexate, azathioprine, and close observation only are becoming more popular [6]; however, potential side effects limit the usage of drug therapy. Moreover, before complete remission, many patients undergo multiple surgical procedures and repeated antimicrobial treatment over months or years, suggesting limited effectiveness of these approaches in GLM.

In this article, we described the clinical presentation, use of antituberculous treatment, and outcomes of 22 patients with GLM.

Methods

Patients

This is a retrospective single-arm clinical assessment study of patients referred to the Second Hospital of Shandong University, China, with a diagnosis of GLM having received antituberculous treatment from January 2011 to Janu-

ary 2015. Patients with any history of malignancy were excluded. Vacuum-assisted biopsy or incisional biopsy was performed depending on the clinical findings at the time of admission. Mammary tuberculosis was excluded by tuberculin skin test, chest radiography, acid-fast staining, and careful histopathologic examination.

Histopathologic Examination

The diagnosis of GLM is based on pathologic findings and must rule out other possible diseases. In this study, histopathologic results were confirmed by 2 pathologists. The specific appearance of GLM is characterized by non-caseating granulomas involving the mammary lobules (fig. 1). Other possible granulomatous inflammatory breast diseases, including Wegener's granulomatosis, granulomatous reaction secondary to sarcoidosis, and foreign body reaction, were excluded.

Clinical and Imaging Findings

The demographic, clinical, and histopathologic data of patients were collected. The imaging findings were assessed in accordance with the Breast Imaging Reporting and Data System (BI-RADS) criteria. Etiologic factors were recorded at the time of presentation, including smoking, alcohol abuse, and body mass index.

Treatment

Lumpectomy or extended lumpectomy were performed in patients who presented with only a breast mass but no erythematous skin changes or fistulae. Patients with breast skin changes or abscess/fistula formation received antibiotics for an average of 7 days (range 5–10 days). After discharge from hospital, triple anti-tuberculosis therapy (rifampicin 0.45 g/day, isoniazid 0.3 g/day, and ethambutol 0.75 g/day) was given to patients for a duration of 6–12 months (fig. 2); liver and kidney function were monitored on a monthly basis.

Follow-Up

Patients were followed monthly for symptoms (e.g., pain and macroscopic appearance of the breast) and side effects of the antituberculous treatment (e.g., nausea, vomiting, and impaired liver function). Changes in mass size and abscess/fistula formation were recorded in detail. Side effects were also recorded during reexaminations. After treatment completion, patients were reviewed every 3 months.

Complete remission was defined as the absence of a breast mass or signs of breast inflammation after finishing medical treatment and no recurrence after 6 months of follow-up. Patients in whom the breast mass did not resolve completely were considered as having partial remission. If there was no change in the breast mass or inflammatory signs at the last clinical visit, the patient was defined as a non-responder [5].

Results

Patient Characteristics

A total of 26 GLM patients were diagnosed and treated in this study. 4 patients received surgical treatment ($n = 3$) or steroid treatment ($n = 1$) and were excluded from analysis. The remaining 22 patients received triple anti-tuberculosis therapy; patient characteristics are summarized in table 1. Tuberculin skin test and chest radiography were negative in all patients, and acid-fast staining was also negative in pathologic sections.

All patients included were ethnic Han women with a median age of 29 years (range 23–44 years). 1 patient was diagnosed with rheumatoid arthritis in the past 4 months, and 1 patient had a history of abdominal tuberculosis (table 2). All patients were married and had 1 or more children (table 2); none had a history of oral contraceptive use.

Fig. 1. Histopathologic findings for granulomatous lobular mastitis. A non-caseating granuloma consisting of lymphocytes, multinucleated giant cells, epithelioid histiocytes, and a small amount of neutrophils, limited to a lobule of the breast (hematoxylin & eosin, $\times 40$).

Fig. 2. Management and treatment of granulomatous lobular mastitis.

Fig. 3. Breast ultrasound presentation of granulomatous lobular mastitis. **A** Irregular hypoechoic mass before treatment; **B** 10 months after treatment with antituberculous therapy.

Clinical and Imaging Presentation

Most patients had unilateral disease (bilateral $n = 1$). Lesions were located in the subareolar region of the breast in 13 patients. The mean size of the mass was 6.03 ± 2.99 cm (range 1.2–12 cm). 2 patients developed erythema of the lower extremities over the course of disease (table 3). Ultrasonography was done in all patients (fig. 3).

Treatment and Outcome

Prior to presenting to hospital, 10 patients did not receive any treatment for GLM. 12 patients received antimicrobial agents orally or by intravenous infusion, including β -lactams (66.7%), macrolides (16.7%), nitroimidazoles (8.3%), and quinolones (8.3%). However, clinical symptoms did not improve with treatment.

Table 1. Demographics, clinical presentation, imaging, treatment, and outcome of 22 patients with granulomatous lobular mastitis

Patient no.	Age at diagnosis, years	Unilateral/bilateral	Size of mass, cm	Subareolar region lesions	Duration of symptoms before diagnosis, months	Ultrasound	Treatment prior to presenting to hospital	Follow-up, months	Outcome
1	27	bilateral	11	yes	3	fluid sonolucent area	antibiotics	53	CR
2	30	right	4	yes	12	hypoechoic mass	none	48	CR
3	34	right	4	yes	3	ductal dilatation	antibiotics	47	CR
4	29	left	4	no	2	mixed-echoic mass	none	lost	–
5	30	right	6	no	0.3	hypoechoic mass	antibiotics	44	CR
6	28	left	3.5	yes	8	mixed-echoic mass	antibiotics	43	CR
7	29	left	7	no	1	hypoechoic mass	antibiotics	43	CR
8	33	right	1.2	yes	1	hypoechoic mass	antibiotics	43	CR
9	27	left	10	no	2	hypoechoic mass	none	43	CR
10	36	right	6	no	0.5	hypoechoic mass	none	42	CR
11	27	right	10	yes	5	ductal dilatation	none	40	PR
12	28	left	5	yes	0.5	hypoechoic mass	none	31	CR
13	42	left	8	yes	12	isoechoic mass	none	30	CR
14	36	left	4	yes	0.5	mixed-echoic mass	none	28	CR
15	44	left	3	no	0.5	hypoechoic mass	antibiotics	27	CR
16	36	left	4	no	0.3	hypoechoic mass	none	26	CR
17	27	right	12	yes	2	fluid sonolucent area	antibiotics	24	CR
18	23	right	3	yes	2	hypoechoic mass	none	lost	–
19	32	right	7	yes	3	normal	antibiotics	lost	–
20	33	right	10	no	2	hypoechoic mass	antibiotics	23	CR
21	28	left	6	no	2	hypoechoic mass	antibiotics	23	CR
22	27	left	4	yes	5	hypoechoic mass	antibiotics	23	CR

CR = Complete remission; PR = partial remission.

After admission, abscess incision and drainage was performed in 1 patient, and small tissue samples were taken during this process for histopathologic examination. Vacuum-assisted biopsy was performed in the remaining 21 patients using the Mammotome™ Biopsy System (Devicor Medical Products, Inc., Cincinnati, OH, USA). For patients with breast skin changes or abscess/fistula formation, a combination of antimicrobial agents (β -lactam plus nitroimidazoles or quinolones plus nitroimidazoles) were used for an average of 7 days (range 5–10 days) to control the acute infection. After pathologic confirmation of GLM, patients received triple anti-tuberculosis treatment according to protocol (fig. 4). There were no severe side effects; however, mild side effects were recorded, including nausea, vomiting, and paresthesia of the fingers or feet.

A total of 3 patients were lost to follow up. For the remaining 19 patients, the median follow-up period was 40 months (range 23–53 months), and the median follow-up period after finishing anti-tuberculosis treatment was 29 months (range 11–42 months). Clinical symptoms improved after 3 months of triple anti-tuberculosis treatment, including mass shrinkage, pain relief, and sinus healing. After treatment completion, all patients underwent physical and ultrasonographic examination to determine outcome. 18 of the 19 patients achieved complete remission; 1 patient did not reach complete remission and retained a mass in her breast. No recurrences or new GLM lesions were observed in the long-term follow-up in all patients.

Discussion

Since GLM was first described as a separate type of breast disease in 1972 [1], many studies, especially in the last decade, have focused on clinical presentation and treatment options [7, 8]. However, so far, the etiology and optimal treatment of GLM are still unclear. In our study, almost all patients were of child-bearing age, and the most common complaint was a breast lump with or without pain. Antituberculous therapy proved to be an effective alternative therapy for GLM in our study.

GLM usually affects women with a history of breastfeeding or recent birth, and our study was consistent in this regard with earlier research. Gestation, breastfeeding, and hyperprolactinemia have been put forward as possible factors underlying the pathogenesis of GLM. Hormonal alterations during these processes, milk secretion, and inflammation have an effect on disease pathophysiology [9, 10]. Other factors related to GLM include oral contraceptives, alcohol abuse, smoking, and ethnic differences [11, 12]; however, in our study, this relationship was not found as none of the patients presented with long-term use of oral contraceptives, alcohol abuse, or active smoking.

GLM was generally associated with clinical symptom of breast lump, abscess, inflammation, and mammary duct fistula or sinus in this study, and this is consistent with the literature [13]; the most common clinical presentation was breast lump with or without skin change and pain, and the most common ultrasonographic

Table 2. Characteristics of patients with granulomatous lobular mastitis

	n (%)
Age, years	
<25	1 (4.55)
25–30	10 (45.45)
30–35	6 (27.27)
35–40	3 (13.64)
≥40	2 (9.09)
Body mass index, kg/m ²	
<24	13 (59.1)
24–28	3 (13.64)
≥28	6 (27.27)
Breast disease history	2 (9.09)
Rheumatoid arthritis	1 (4.55)
Smoking	0 (0)
Passive smoking	11 (50)
Alcohol abuse	0 (0)
Age at birth of first child, years	
<25	5 (22.73)
25–30	14 (63.64)
≥30	3 (13.64)
Parity, n	
1	17 (77.27)
2	5 (22.73)
Abortion, n	
0	13 (59.09)
1	4 (18.18)
≥2	3 (13.64)
Previous delivery, years	
<3	8 (36.36)
3–5	7 (31.82)
≥5	7 (31.82)
Duration of breastfeeding, months	
<12	3 (13.64)
12–24	11 (50)
≥24	5 (22.73)
Pregnancy but no lactation	3 (13.64)
No lactation from the affected side	6 (27.27)
Age at menarche, years	
<14	11 (50)
≥14	11 (50)
Menopause	1 (4.55)

finding was a large irregular hypoechoic mass. In the absence of specific radiologic findings, the diagnosis of GLM is based on histopathologic findings.

There is no standard GLM treatment so far. Observational management, surgical intervention, and medical treatment are common modes of therapy [14]. Surgical intervention should be used with caution as a 16–50% recurrence rate was reported after surgical treatment [11]. To date, administration of corticosteroids for large lesions prior to surgery is recommended to help minimize lesion size and obtain better cosmetic outcome [15].

As for pharmacotherapy, corticosteroids have been used as primary treatment after surgery to prevent GLM recurrences [9]. Others have recommended that corticosteroid treatment should be used only in complicated cases because of its side effects [16]. Yabanoglu et al. [17] indicated that wide surgical excision might be

Table 3. Clinical characteristics and presentation of patients with granulomatous lobular mastitis

Mean size of mass, cm	6.03 ± 2.99
	n (%)
Affected side	
Left	11 (50)
Right	10 (45.45)
Bilateral	1 (4.55)
Quadrant(s)	
Upper-outer	4 (18.18)
Lower-outer	1 (4.55)
Upper-inner	5 (22.73)
Lower-inner	1 (4.55)
2 or more quadrants	11 (50)
Subareolar region lesions	13 (59.09)
Clinical presentation	
Mass without pain	12 (54.55)
Mass with pain	10 (45.45)
Erythematous skin	16 (72.73)
Nipple discharge	1 (4.55)
Sinus formation	8 (36.36)
Axillary lymphadenopathy	10 (45.45)
Nipple retraction	6 (27.27)
Erythema in lower extremities	2 (9.09)

the preferred approach, while the recurrence rate with steroids was much higher. Recently, topical corticosteroids were also reported to be effective in the management of GLM [18]. However, most of these conclusions are based on small case series and have not been confirmed epidemiologically. Moreover, because of the potential side effects of corticosteroids, their application is limited. Immunosuppressive agents like methotrexate and azathioprine are also thought to have some value in the treatment of GLM [19], based on the perception of GLM as an autoimmune disease.

In a recent review article, Lei et al. [20] evaluated the complete remission/resolution and recurrence rates of different treatment options. 6, 9, and 5 studies with 138, 358, and 106 patients were analyzed for surgical management, oral steroids, and oral steroids plus surgical managements, respectively. The pooled estimates for complete remission rate were 90.6, 71.8, and 94.5%; the pooled estimates for recurrence rate were 6.8, 20.9, and 4.0%, respectively. In our study, the complete remission rate with antituberculous therapy was 94.7% (18/19), while no recurrence was observed. However, given the limited case numbers and follow-up time, further investigations are needed to better understand the role of antituberculous therapy in the managements of GLM.

Observational management may also be an acceptable approach, because more than half of the patients with GLM who did not receive any treatment were found to achieve complete remission [21]; however, it should be noted that patients were symptomatic for longer before reaching remission. Bouton et al. [3] considered GLM as a self-limiting benign condition, and they found the average time to resolution to be 7.4 months, albeit with a recurrence rate of 11%.

In this study, antituberculous therapy was found to be an effective alternative treatment for patients diagnosed with GLM. Others have also reported antituberculous therapy in the treatment of

Fig. 4. Clinical presentation of a patient with granulomatous lobular mastitis and treatment with anti-tuberculous therapy. **A** Clinical presentation; **B** 1 month after antituberculous therapy; **C** 2 months after treatment; **D** 5 months after treatment.

GLM: Rao et al. [22] reported that of 34 patients who completed an antituberculous treatment regimen, 33 were cured without additional surgical intervention. Velidedeoglu et al. [23] also found that antituberculous treatment was effective in the treatment of a patient with bilateral disease. Recently, Farouk et al. [24] reported that in their prospective study including 30 GLM patients, rifampicin (300 mg twice daily for 6–9 months) was an effective

therapy. In contrast, Sheybani et al. [7] recently reported that 7 patients who also had a history of complete or incomplete antituberculous treatment showed symptom deterioration and no response to medication.

A relationship between GLM and *Corynebacteria* was first reported by Binelli et al. [25] in 1996, and reports pertaining to this link have increased over the years [26, 27]. *Corynebacteria*, especially *C. kroppenstedtii*, have been accepted as possible pathogens by some authors [28]. Interestingly, Dobinson et al. [14] conducted an antimicrobial susceptibility test for common antibiotics, and results indicated that *C. kroppenstedtii* was susceptible to rifampicin and resistant to β -lactams.

In conclusion, our results indicate that antituberculous therapy may be an effective and appropriate alternative treatment options for GLM in a number of situations. Further studies with higher patient numbers are needed to evaluate the efficacy of antituberculous therapy, and the effect must be assessed in long-term follow-up.

Disclosure Statement

This study was supported by the National Health and Family Planning Commission's Public-Benefit Project (201502027) and the Jinan City Clinical Medical Innovation Project (201602146).

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