Management of Lobular Granulomatous Mastitis; Special Focus on Treatment Challenges in Patients with Hyperprolactinemia, Erythema Nodosum, and Diabetes, and Factors Associated with a Persistent Disease Course

Mina Akbari Rad
Mashhad University of Medical Sciences
Abdollah Firoozi
Mashhad University of Medical Sciences
Fereshte Sheybani
Mashhad University of Medical Sciences
Samaneh Sajjadi
Mashhad University of Medical Sciences
Maryam Emadzadeh
Mashhad University of Medical Sciences
Marzieh Kazerani
Islamic Azad University
Sajad Ataei Azimi
Mashhad University of Medical Sciences
Mahdieh Mottaghi
mahdiehmottaghii@gmail.com

Mashhad University of Medical Sciences

Research Article

Keywords: Granulomatous Mastitis, Mastitis, Treatment Outcome, Diagnosis

Posted Date: April 12th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4230702/v1

Additional Declarations: No competing interests reported.

Abstract

Background

This study presents our observations on the management of patients with lobular granulomatous mastitis (LGM) in a cohort study. Additionally, characteristics associated with a longer disease course, as well as treatment challenges in patients with erythema nodosum, diabetes, and hyperprolactinemia would be discussed.

Methods

From 2015 to 2021, a total of 246 consecutive LGM patients referred to Ghaem teaching hospital, Mashhad, Iran, were treated and followed up every three months until complete symptom resolution. Treatment responses were categorized into five groups: complete resolution, incomplete resolution, resolution with subsequent relapse, no significant improvement, and treatment cessation. Telephone follow-ups were conducted with all patients at the end of the study in December 2022. The primary outcome was the response to treatment with prednisone or methotrexate (MTX). The secondary outcome was response to treatment by the last telephone follow-up.

Results

Among the initial 246 patients, 90 were excluded, and a total of 156 episodes were analyzed. Prednisone was administered to 136 patients, while oral MTX was prescribed to 48 cases. The median age of the cohort was 33 years (interquartile range [IQR], 29–38). The primary outcomes were as follows: Of those on prednisone, 57 (41.9%) achieved complete resolution, with 15 (11%) experiencing subsequent relapse, 33 (24.3%) showing no significant improvement, and 31 (19.9%) discontinuing treatment. Among the MTX recipients, 23 (47.9%) achieved complete resolution, while one showed incomplete resolution. The secondary outcomes were complete resolution in 139 (89.1%), incomplete resolution in nine (5.8%) showed, and 8 (5.1%) cases remained symptomatic. The median disease duration was 18 months (IQR, 7–36), with a median follow-up period of five years (IQR, 4–6). Abscess formation during treatment correlated with prolonged disease duration ($p < 0.04$), and higher plasma prolactin levels were associated with extended disease duration ($p = 0.001$). However, the disease course did not significantly differ in diabetic cases or those with erythema nodosum compared to others.

Conclusions

Over a median follow-up of five years, approximately 90% of LGM patients achieved complete resolution within a median course of 18 months. The presence of abscesses during treatment and elevated plasma prolactin levels were linked to longer disease duration.

INTRODUCTION

Lobular granulomatous mastitis (LGM) manifests as a benign inflammatory condition characterized by the formation of non-necrotizing granulomas within the breast tissue. While it predominantly affects women who have given birth and have a history of breastfeeding (1), cases have also been documented in nulliparous women and men (2). Several studies have suggested an autoimmune mechanism underlying the development of LGM (3, 4). Additionally, environmental factors such as trauma, hormonal changes, metabolic fluctuations, leakage of lactational secretions, and infection with Corynebacterium species have been proposed as potential triggers for LGM (4–7).

While lobular granulomatous mastitis (LGM) may resolve on its own, especially in mild instances, it often presents significant debilitation (8–10), warranting treatment for symptom management and cosmetic concerns. Corticosteroids (CSs) have demonstrated efficacy in treating LGM, although the optimal dosage and duration remain debated (1, 11, 12). Other anti-inflammatory medications, such as methotrexate (MTX), azathioprine, and mycophenolate mofetil, have also been utilized in LGM treatment (13–15).

In this cohort study, we describe the demographic characteristics, clinical presentations, treatment strategies, and clinical outcomes of 156 patients diagnosed with LGM.

METHODS

Patients

This prospective cohort study enrolled patients diagnosed with pathologically confirmed LGM who were referred to the internal medicine clinic of Ghaem Teaching Hospital in Mashhad, Iran, between January 2015 and December 2021. To exclude secondary etiologies, tuberculin skin tests, bacterial, mycobacterial, and fungal staining and cultures, as well as polymerase chain reaction (PCR) testing for Mycobacterium tuberculosis, were conducted. Plasma levels of angiotensin-converting enzyme (ACE), prolactin, fasting blood sugar (FBS), and erythrocyte sedimentation rate (ESR) were measured for all patients.

Individuals with follow-up periods of less than one year, those diagnosed with tuberculosis mastitis, and male patients were excluded from the study. Data regarding patient history, presenting symptoms and signs, laboratory and imaging results, treatment regimens, and outcomes were collected to achieve the following objectives: 1) assess treatment management and outcomes in LGM patients, 2) evaluate the impact of LGM in individuals with diabetes, hyperprolactinemia, and erythema nodosum (EN), and 3) identify characteristics associated with a prolonged disease course.

Ethical Considerations

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences under project numbers 4010734 and the ethics codes of IR.MUMS.MEDICAL.REC.1401.609. All patients were included in the study with informed consent.

Treatment approaches

All patients received detailed information regarding the disease's prolonged and self-limiting nature, which typically resolves gradually over time. Treatment modalities included the administration of prednisone, MTX, or referral to a surgeon (Fig. 1). Prednisone therapy commenced at a dosage ranging from 0.5 to 1 mg/kg/day, adjusted according to the severity of symptoms, and typically continued for 2–4 weeks. Subsequently, patients underwent regular physical examinations every three months following the initiation of treatment. Treatment outcomes were classified into five distinct categories: complete resolution, partial resolution, recurrence, persistence, and treatment cessation (Table 1).

Table 1
Classification of "Response to Treatment" in Patients with Lobular Granulomatous Mastitis

Complete resolution	**Disappearance of breast mass(es) upon physical examination and substantial reduction in inflammatory signs and symptoms.**
Partial resolution	Significant decrease in breast mass(es) size upon physical examination or improvement in inflammatory signs and symptoms, but not complete resolution.
Recurrence	Initial disappearance of breast mass(es) upon physical examination and notable reduction in inflammatory signs and symptoms, followed by recurrence within at least one month.
Persistence	Continued presence of signs and symptoms without significant improvement.
Treatment cessation	Decision to discontinue management.

In cases where symptoms completely resolved, the dosage of prednisone was gradually tapered by 5 mg per week. Conversely, for patients with incomplete resolution, prednisone was tapered more gradually, at a rate of 5 mg every 2–3 weeks. After achieving complete symptom resolution, patients ceased follow-up appointments but were advised to return to the clinic if signs or symptoms recurred. If symptoms reappeared during or after the tapering of corticosteroids, another course of prednisone was prescribed. Those who discontinued treatment were monitored via telephone follow-ups.

For individuals showing no significant improvement on corticosteroids, prednisone was tapered off and oral MTX was initiated at a dosage of 5–20 mg per week, adjusted according to symptom severity. All patients on MTX received daily folic acid supplementation at a dose of 5 mg. Follow-up appointments were scheduled every three months, during which regular check-ups for complete blood count (CBC) and liver function enzymes were conducted. Treatment response was evaluated using previously outlined criteria. Upon resolution of symptoms, MTX dosage was gradually reduced by 2.5 mg per week, with patients advised to return to the clinic only if symptoms recurred. Patients who did not respond to oral MTX received subcutaneous MTX at the same dosage range and continued follow-up as instructed.

In cases of persistent severe inflammatory symptoms despite treatment with prednisone and/or MTX, surgical excision of the lesion (lumpectomy) was performed. Patients experiencing abscess formation underwent incision and drainage.

Telephone follow-up was conducted at the end of the follow-up period in December 2022. Patients were queried about their symptoms, any episodes of relapse, treatment side effects, and other types of treatments they might have pursued. If patients reported mastitis symptoms or side effects, they were advised to return to the clinic for further clinical assessment. The duration of the disease was defined as the time interval between symptom onset and complete recovery without subsequent relapse.

Primary and Secondary Outcome

The primary outcome of the study was to determine the status of response to treatment with prednisone, oral MTX, subcutaneous MTX, and surgery. The secondary outcome was to evaluate the status of the response to treatment by the last telephone follow-up.

Statistics and Sample Size

Data analysis was done using IBM SPSS statistics version 22 software. Continuous data were presented as medians with interquartile range [IQR] (25th to 75th percentile), while categorical variables were expressed as frequencies and percentages. Normal distribution was evaluated using the one-sample Kolmogorov-Smirnov test. For continuous variables with non-normal distribution, the Mann–Whitney U-test was employed for comparison, whereas Fisher's exact test and chi-square tests were utilized for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant. Correlation analysis was conducted using the Spearman test. The sampling method employed was consecutive, with all eligible patients included in the study.

RESULTS

Out of the initial 246 patients diagnosed with LGM and included in our study, 67 were excluded due to incomplete documentation, 18 patients missed subsequent follow-ups, four were diagnosed with tuberculosis mastitis, and one male patient was excluded. Consequently, our analysis focused on 156 female patients with idiopathic LGM.

Patients

The median age of the cohort was 33 years (IQR, 29–38), with 96.2% of patients being married. The median number of children was two (IQR, 1–3), with eight cases being nulliparous. Fifteen patients (9.6%) were using hormonal contraception, and five (3.2%) reported a history of trauma to the affected breast. The median interval between the onset of symptoms and referral to our clinic was 90 days (IQR, 60–180). Twenty-one patients (13.5%) had experienced previous episodes of IGM. Clinical findings at the initial appointment included breast mass in 114 cases (73.1%), pain/tenderness in 102 cases (65.4%), erythema in 56 cases (35.9%), nipple retraction in 41 cases (26.3%), discharge in 42 cases (26.9%), and axillary lymphadenopathy in 27 cases (17.3%). The discharge was from a sinus tract to the lesion surface in 27 patients, from the nipple in 10 cases, and from the biopsy site in five patients. Five cases reported purulent discharge. Symptoms were unilateral in 126 patients (80.8%), while subsequent involvement of

the second breast occurred in 30 patients (19.2%). Ultrasound examination revealed a mean mass size of 2.6 cm, with 18 cases (11.5%) having a breast mass larger than 5 cm. Extra-mammary manifestations included fever at disease onset in 11 patients (7.1%), erythema nodosum in 8 patients (5.1%), and peripheral arthritis in 14 patients (9%).

At the initial appointment, 43 cases (28.1%) were diagnosed with a breast abscess, while 50 patients (32.1%) developed an abscess from the breast mass during treatment. The average plasma levels of prolactin in non-pregnant patients, ACE, and ESR were 12.7 (IQR, 7.9–21) ng/dl, 38 (IQR, 26-51.2) U/L, and 25 (IQR, 13.75–45.25) mm/h, respectively.

Primary outcome

In total, prednisone was administered as the primary treatment to 136 patients (87.2%), ranging from 3–60 months. Thirteen cases (8.3%) had previously undergone surgery for excision of the breast mass, while 12 patients (7.7%) had received incision and drainage for the lesion. Among those treated with corticosteroids, complete resolution was observed in 57 patients (41.9%), 15 patients (11%) experienced resolution followed by relapse, and 33 patients (24.3%) showed no significant improvement. Thirty-one cases (22.8%) discontinued treatment, with 21 attributed to poor compliance, eight due to adverse medication effects, and two due to pregnancy.

Follow-up calls with patients who discontinued prednisone revealed that 15 cases were referred to a surgeon for lumpectomy, with 8 undergoing incision and drainage of the lesion, while the remaining 16 cases opted for conservative management. Adverse effects attributed to corticosteroid use were observed in 25 patients (18.4%), leading to treatment cessation in 8 individuals. These adverse reactions included weight gain in 14 cases, high blood sugar in five, proximal myopathy in three, and diarrhea, hemangioma, and hypertension, each occurring once.

Out of the 48 cases who were administered MTX, either as the primary treatment or as an alternative regimen, complete resolution of symptoms was observed in 23 patients (47.9%), while one patient experienced incomplete resolution. Resolution followed by recurrence was noted in 5 cases (10.4%), and 12 patients (25%) showed no discernible improvement. Seven patients discontinued oral MTX; five due to poor compliance, one due to pregnancy, and one due to side effects.

Follow-up phone calls with patients who discontinued oral MTX showed that six cases opted for conservative management, while one patient was referred to a surgeon for incision and drainage of the lesion.

MTX-related side effects were reported in three patients (6.2%), with one patient discontinuing the treatment. These side effects included nausea in two patients (4.2%) and an increase in liver enzymes in one patient. Switching from oral MTX to the subcutaneous form resolved the side effects in two patients, but in one case, the side effects were severe enough to warrant discontinuation of the treatment.

In total, twelve patients (8.8%) were administered subcutaneous MTX, with nine cases (75%) experiencing complete resolution of symptoms. However, two patients (16.7%) did not show significant improvement, and one patient (8.3%) discontinued treatment.

Lastly, two patients (1.3%) who did not achieve complete resolution with steroid and MTX treatment underwent surgical lumpectomy.

Secondary outcome

The final follow-up was conducted via telephone in December 2022. Patients were questioned about their symptoms, any episodes of relapse, or treatment side effects. Those reporting mastitis symptoms or adverse effects were advised to visit the clinic for further evaluation. The median follow-up duration was 5 years (IQR, 4–6 years).

By the end of the study, 139 patients (89.1%) reported complete resolution, while 9 patients (5.8%) exhibited incomplete resolution, and 8 cases (5.1%) continued to experience symptoms. The median duration of the disease was 18 months (IQR, 7–36), with a range from 2 to 126 months.

Factors Linked to Prolonged Illness Duration

Patients who developed breast abscesses after treatment had a notably longer illness duration compared to those who did not experience such complications (median duration of 23 [IQR, 11–44] months versus 12 [IQR, 6-30.5] months, P = 0.04). No significant associations were found between other characteristics and extended illness duration (see Table 1).

Table 1
Overview of demographic data, clinical symptoms, and median illness duration among patients diagnosed with lobular granulomatous mastitis (n = 156).

Characteristics	Frequency (%)	Median duration of the disease, months (IQR, %25, %75)	*p* value
Demographic features			
Marital status	150 (96.2%)	18 (7, 36.25)	0.97
Married		18 (9, 35.5)	
Single	6 (3.8%)		
History			
Oral contraceptive	15 (9.6%)	22 (10, 37)	0.61
Positive		18 (7, 36)	
Negative			
Family history of breast cancer	12 (7.7%)	13 (6, 29.25)	0.40
Positive		18 (7.75, 36.25)	
Negative			
Pattern of involvement			
Bilateral	30 (19.2%)	23 (12, 49.5)	0.07
Positive		14.5 (7, 36)	
Negative			
Clinical manifestations			
Mass	114 (73.1%)	20 (8.25, 36.5)	0.62
Positive		12 (6.75, 32.25)	
Negative			
Mass > 5cm on sonography	18 (11.5%)	21 (6.75, 37.25)	0.78
Positive		18 (7, 36)	
Negative			
Abscess	43 (27.6%)	22 (11, 48)	0.19
Positive		13 (6, 36)	
Negative			

Characteristics	Frequency (%)	Median duration of the disease, months (IQR, %25, %75)	*p* value
Pain	102 (65.4%)	18 (9.75, 36.5)	0.30
Positive		12 (6, 35.5)	
Negative			
Erythema	56 (35.9%)	24 (7.5, 41.75)	0.13
Positive		12 (7, 30)	
Negative			
Nipple retraction	41 (26.3%)	24 (9, 51)	0.10
Positive		16.5 (7, 32)	
Negative			
Discharge from an open wound/ fistula/nipple	42 (26.9%)	22 (9, 44)	0.24
Positive		15 (7, 36)	
Negative			
Axillary lymphadenopathy	27 (17.3%)	24 (12, 48)	0.19
Positive		18 (7, 36)	
Negative			
Abscess formation following treatment	50 (32.1%)	23 (11, 44)	0.04*
Positive		12 (6, 30.5)	
Negative			
Erythema nodosum	8 (5.1%)	24 (13.5, 43.5)	0.42
Positive		18 (7, 36)	
Negative			

The disease duration was defined as the time elapsed between the onset of symptoms and achieving complete recovery without any subsequent relapse. * $p < 0.05$ considered statistically significant

Abbreviations IQR: inter quartile range

LGM and hyperprolactinemia/ Prolactinoma

Twenty patients (12.8%) exhibited elevated levels of plasma prolactin (normal range 4.8–23.3 ng/mL), with no history of pregnancy or prior medication use. Brain magnetic resonance imaging (MRI) revealed pituitary adenomas in four cases (2.6%). Patients with lobular granulomatous mastitis (IGM) and hyperprolactinemia experienced a prolonged disease course compared to those with normal plasma prolactin levels (35.5 [IQR, 18.5-60.75] months versus 13 [IQR, 7–30] months, P = 0.001). These patients were treated with bromocriptine or cabergoline, as outlined in Table 2.

Table 2
Overview of treatment strategies employed in patients with prolactinoma (n = 4).

Patient	Plasma Prolactin levels (ng/dl)	The course of the disease (months)	MRI findings	Treatment approaches
1	69	48	prolactinoma	Prednisone, oral, and subcutaneous MTX failed to prevent relapse, leading to the patient being referred to a surgeon for breast lumpectomy. Eventually, remission was attained.
2	112	31	prolactinoma	Prednisone was initiated, ultimately resulting in remission.
3	114	20	prolactinoma	Prednisone and oral MTX failed to prevent relapse. Subcutaneous MTX was initiated, ultimately resulting in remission.
4	201	54	prolactinoma	Prednisone, oral and subcutaneous MTX, as well as surgery (breast lumpectomy), all failed to prevent relapse. Ultimately, repeated incision and drainage of the lesion led to remission.

Plasma prolactin levels exceeding 23.3 ng/mL are considered indicative of hyperprolactinemia.

Abbreviations MRI: Magnetic resonance imaging, MTX: Methotrexate, SC: subcutaneous

LGM and Diabetes Mellitus

Out of the 156 patients enrolled in this study, 12 (7.7%) had a medical history of diabetes mellitus. The median duration of symptoms until complete remission in patients with diabetes compared to non-diabetic individuals was 24 months (IQR, 11.25–36.75) versus 18 months (IQR, 7–36), respectively, with no significant difference observed (P = 0.61). Two of these patients exhibited elevated plasma prolactin levels attributed to lactation and prolactinoma. Details of the treatment approaches are outlined in Table 3.

Table 3
Overview of treatment strategies employed in patients with diabetes (n = 12).

Patient	FBS (mg/dl)	HgA1C (mg/dl)	Course of the disease (months)	Treatment approaches
1	75		3	A 72-year-old patient underwent expectant management, leading to remission.
2	108	6.1	37	Prednisone was initiated, ultimately resulting in remission. The patient had elevated plasma levels of prolactin.
3	127	7.5	36	Prednisone treatment was commenced, leading to remission.
4	154		11	Prednisone (20 mg/day) administration resulted in elevated fasting blood sugar (FBS) levels. The treatment was discontinued, and conservative management was initiated, involving wound drainage with traditional medicine, ultimately resulting in remission.
5	161	5.7	24	Prednisone treatment led to elevated FBS levels. Subsequently, MTX therapy was initiated, resulting in remission.
6	175	7	3.5	Prednisone treatment led to remission.
7	217	9.9	12	Prednisone resulted in elevated FBS levels. MTX therapy was initiated, leading to remission.
8	267		60	The patient had a history of LGM and underwent lumpectomy, followed by recurrence during pregnancy, which resolved with expectant management.
9	285	12.1	24	Initially, MTX therapy was initiated, but recurrence occurred despite two years of treatment. The therapy was discontinued, and conservative management, involving physical drainage of the wound, was initiated, resulting in remission 10 months later.
10	294	8.6	12	Prednisone treatment led to remission.
11	330	12.1	54	Prednisone treatment led to elevated FBS levels. Subsequently, MTX therapy was initiated, resulting in relapse. Conservative management involved wound incision and drainage, ultimately leading to remission. The patient had a history of prolactinoma.
12	341	12.1	36	MTX therapy was initiated, leading to remission.

Abbreviations AB: Antibiotic, FBS: Fasting blood sugar, Hg A1C: Hemoglobin A1C, MTX: Methotrexate.

LGM and Erythema Nodosum

In our study, eight cases (5.1%) presented with both LGM and erythema nodosum (EN). Managing symptoms in this subgroup posed greater challenges, with half of the patients (four out of eight) having experienced a prior episode of LGM. Additionally, the disease manifestation was more complex, with five patients (62.5%) exhibiting multiple breast masses, and one case (12.5%) involving both breasts. Furthermore, half of the cases (four out of eight) experienced concurrent arthritis and EN alongside LGM.

Among the eight cases receiving steroid treatment for LGM and EN, five cases experienced healing, while two encountered recurrences. For the three patients who showed no improvement with prednisone, and one who experienced recurrence, oral MTX was administered. Out of the four cases receiving oral MTX, two did not show improvement, and one experienced recurrence, prompting all three to switch to subcutaneous MTX. Ultimately, all cases achieved complete recovery.

The disease course in patients with both LGM and EN was observed to be 24 months (IQR, 13.5–43.5), compared to 18 months (IQR, 7–36) in those without EN; however, this difference was not statistically significant (P = 0.42).

DISCUSSION

Our study showed that the treatment management and outcomes in patients with LGM present a complex clinical scenario. With the rising global incidence of LGM cases, the complexities in managing patients become increasingly apparent, particularly among special groups such as those with underlying medical conditions. **In our study, corticosteroids, as the primary treatment, was administered to a majority of patients, showing varying degrees of effectiveness and tolerability. Among those treated with corticosteroids, a notable proportion (42%) experienced complete resolution of symptoms, while others faced relapse (11%) or showed no improvement (24%). Additionally, a significant number of patients discontinued corticosteroids due to reasons such as poor compliance, adverse medication effects, or pregnancy.** Previous research has presented varying rates of treatment success among LGM patients receiving corticosteroids either alone or combined with other treatment modalities. A meta-analysis involving 358 LGM patients treated with oral corticosteroids between January 1, 2010, and December 31, 2015, showed complete remission rates ranging from 30.8–100%, with recurrence rates ranging from 0–46.2%. The pooled estimates for complete remission and recurrence rates of corticosteroids were 71.8% [95% CI (confidence interval) 67.1%, 76.3%] and 20.9% (95% CI 9.2%, 16.1%), respectively. When oral corticosteroids were combined with surgery, the estimated complete remission and recurrence rates were 94.5% (95% CI 88.9%, 98.3%) and 4% (95% CI 1.5%, 8.4%), respectively (16). In another systematic review and meta-analysis covering corticosteroids in LGM involving 559 patients up to May 21, 2019, the recurrence rate in the corticosteroids -only group was 17.7%. The relative risk and risk difference of recurrence in the steroid-only group compared with the surgery-only group were 2.99 (95% CI 0.28–31.33) and 0.14 (95% CI − 0.01–0.30), respectively, showing no significance. Additionally, the relative risk of recurrence in the corticosteroids-only group compared to the combined therapy of corticosteroids plus surgery was 6.13 (95% CI 0.41–81.62), again showing no significance. However, the risk of recurrence in the steroid-only group was significantly higher than in the corticosteroids plus surgery group (risk

difference: 0.28, 95% CI 0.11–0.44) (16). Administering corticosteroids as an adjunctive therapy prior to surgical interventions in patients with LGM has also demonstrated effectiveness in reducing inflammation (17). A study involving 156 patients who received 5 days of in-patient steroid therapy before excisional surgery revealed that only 5.1% of them experienced recurrence, a significantly lower rate compared to those who solely received prednisone ($p < 0.01$) (18). In addition to systemic steroid administration, the utilization of topical steroid application and intralesional injections has also shown promising results (19, 20).

Adverse effects attributed to corticosteroid in a considerable proportion of patients who discontinued treatment in our study underscore the need for close monitoring and management of side effects in LGM treatment. It also highlights the difficulties linked with prolonged corticosteroid treatment in managing LGM, emphasizing the need for additional research into alternative steroid-sparing therapies for this condition.

In situations where corticosteroid therapy proved insufficient or was not well-tolerated, MTX was prescribed as an alternative treatment option. Oral MTX is commonly employed as a second-line therapy for patients with IGM who either do not respond to or cannot tolerate steroids (12). **While MTX showed promising results in half of our patients, approximately 10% experienced recurrences during follow-up. Moreover, MTX-related side effects were reported, leading to treatment discontinuation in some other cases.** Adverse reactions to MTX have been documented in previous studies, ranging from none to 18.2% (21–23). However, in our cases, side effects were observed in only about 5% of patients. Retrospective analyses have reported remission rates ranging from 75–100% and recurrence rates between 12.5% and 15.8% with MTX monotherapy, typically administered at doses of 7.5 to 25 mg per week over an average treatment duration of 8.5 to 15 months (13, 23, 24). **The choice between oral and subcutaneous MTX administration depends on individual patient factors and tolerability.**

Literature indicates that MTX is often used in conjunction with corticosteroids. Combining prednisone with MTX at doses of 5 to 10 mg per week has led to remission rates ranging from 58.5–100%, with relapse rates varying from zero to 28.6% (21, 22, 24–28). Discrepancies in outcomes of our patients compared to previous studies may be attributed to the inclusion of treatment discontinuation as a separate category within treatment outcomes. While some patients who discontinued treatment experienced improvement due to the self-limiting nature of the disease, they were classified as treatment discontinuation cases rather than being included in the remission group.

A small subset of patients in our study eventually required surgical intervention, such as lumpectomy, indicating the refractory nature of the disease in certain cases. Surgical resection is often regarded as the most efficient treatment approach in LGM with the shortest resolution time. A meta-analysis revealed that surgical excision significantly increased the complete remission rate compared to steroid therapy ($P = 0.0003$). However, the study reported no significant difference in effectiveness between observation and surgical intervention for early LGM patients with mild symptoms (relative risk (RR) = 0.78, 95% CI [0.55, 1.11], $P = 0.17$) (29). Another meta-analysis reported a recurrence rate of 22.5% for various surgical

procedures including drainage, excision, and lumpectomy (30). Moreover, surgical procedures carry potential complications such as impaired wound healing, fistula or abscess formation (ranging from 4.7–30.0%), scarring, and breast asymmetry. These factors have led surgical intervention to be considered an alternative approach for patients who do not respond to medical therapy rather than being the primary management option (31–37).

Upon our final follow-up conducted after a median duration of five years, we discovered that over 90% of LGM patients achieved complete resolution of their symptoms, irrespective of the treatment approaches utilized. Similarly, a meta-analysis revealed that 95.5% of LGM patients with mild symptoms experienced spontaneous resolution (29). While **secondary outcome of the study, assessed through long-term follow-up, demonstrated a high rate of complete resolution among our patients**, underscoring the self-limiting nature of LGM, it's important to note that we did not conduct a comparative analysis to assess the severity of mastitis at presentation and the cosmetic outcomes between patients receiving medical treatment and those managed conservatively. Moreover, **a proportion of patients continued to experience symptoms or exhibited incomplete resolution during the study follow-up, emphasizing the chronic and variable nature of LGM.**

There has been considerable debate regarding the optimal approach to managing LGM, whether it should be actively treated or managed through observation, and the most effective treatment modality for those who require intervention: medical or surgical. LGM is categorized into four stages based on disease progression and clinical presentation: (1) self-limited stage, (2) congestive swelling stage, (3) abscess formation stage, and (4) complex refractory stage. At the self-limited stage, and watchful waiting through clinical examination has been proposed as a reasonable strategy. During this stage, symptoms may spontaneously resolve or remain stable for months or even years (38). In our study, 11 (7%) cases initially underwent expectant management and showed improvement over a median period of approximately 10 months. Similarly, previous research has indicated that in patients who were observed without active treatment, symptom resolution typically occurred within a range of 5 to 14.5 months (8–10, 39–41). Davis et al. observed that delayed first childbirth was correlated with a longer duration of watchful waiting (8).

Several factors have been identified as contributors to the more persistent course of LGM. **In our investigation, elevated prolactin levels and the occurrence of breast abscesses subsequent to treatment were linked to prolonged mastitis duration. Patients who developed breast abscesses post-treatment exhibited a substantially longer illness duration compared to those who did not experience such complications. The median duration of illness in this subgroup was 23 months, significantly longer than the median duration of 12 months observed in patients without abscess formation. This association underscores the clinical significance of abscess development as a marker of disease severity and complexity.** Similarly, prior research has shown that the recurrence of LGM is more prevalent among those who develop recurrent abscesses during treatment (42). **The prolonged illness duration in patients with abscesses may be attributed to factors such as delayed healing and the need for additional interventions such as surgical drainage.**' Hur et al. demonstrated that patients with lesions measuring 1–2 cm in

diameter tended to experience a self-limited condition, while those with larger lesions (> 5 cm) were more prone to progress to breast abscess (39). O**ur study did not identify significant associations between other characteristics and extended illness duration. Characteristics like marital status, the use of hormonal contraceptives, a family history of breast cancer, and clinical signs such as the presence of a mass, erythema, nipple discharge, axillary lymphadenopathy, EN, and the size of the mass did not demonstrate statistically significant associations with the duration of the disease.** Previous studies have indicated that purulent nipple discharge, skin lesions, bilateral disease, pain, a Body Mass Index (BMI) of ≥ 24 (indicative of overweight/obesity), and an elevated follicle-stimulating hormone (FSH)/luteinizing hormone (LH) ratio are associated with a heightened risk of recurrence (43–46). Our findings demonstrated that although patients experiencing pain, nipple retraction, fistula drainage, and bilateral involvement tended to have a longer disease duration, these differences did not reach statistical significance. **While some of these factors may contribute to disease pathogenesis and presentation, they may not independently influence the duration of illness in LGM patients.**

LGM can present unique challenges in individuals with comorbidities such as diabetes mellitus, hyperprolactinemia, and erythema nodosum (EN). **Our study investigated the impact of these comorbid conditions on the disease course and treatment outcomes in LGM patients. Elevated levels of plasma prolactin were observed in a subset of patients, with a notable proportion exhibiting pituitary adenomas. Patients with LGM and hyperprolactinemia experienced a prolonged disease course compared to those with normal prolactin levels, emphasizing the influence of hormonal factors on disease progression. Treatment with bromocriptine or cabergoline was effective in managing hyperprolactinemia-associated LGM, highlighting the importance of addressing underlying hormonal imbalances in treatment strategies**. Consistent with our findings, previous studies have also suggested an association between elevated prolactin levels and the recurrence of LGM (45, 47). Elevated prolactin levels can lead to increased milk production and accumulation within the mammary lobules, potentially causing infection or extravasation into the perilobular stroma, triggering a T-cell-mediated immune response and subsequent granuloma formation (48). Moreover, prolactin has been shown to activate the nuclear factor kappa-light-chain-enhancer of activated b cells (NF-kB) signaling pathway in mammary epithelial cells, leading to the production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, (tumor necrosis factor) TNF-a, interferon (INF)-c, and Granulocyte macrophage colony stimulating factor (GM-CSF), which could further exacerbate inflammation and contribute to granuloma formation in the breast (49). Thus, elevated prolactin levels may exacerbate inflammation and influence the duration of recovery, underscoring the importance of routine screening for hyperprolactinemia in LGM patients (9, 50).

In our study, 12.8% of LGM patients exhibited elevated plasma prolactin levels. A meta-analysis conducted in 2023 reported a prevalence of hyperprolactinemia in 19.7% of LGM patients (99 out of 502) (30). **Furthermore, 2.6% of our cases were diagnosed with prolactinoma. This finding suggests an unusually high prevalence of prolactinoma among LGM patients** compared to the incidence of 60–100 cases per 1,000,000 individuals in general population (51).

Treating LGM in special patient groups, such as those with diabetes, poses notable challenges. Although diabetes has been reported in 6.2% of LGM cases, no clear association has been established between diabetes and the onset or recurrence of LGM (44). Hyperglycemia is known to result in the formation of glycosylated end products that may stimulate B-cell proliferation and cytokine release, leading to an autoimmune response in various organs, including the breasts (52). It is also suggested that persistent hyperglycemia, along with increased intermolecular cross-linkage and glycosylation, impedes collagen degradation, contributing to connective tissue accumulation in the breasts (53). **In our study, diabetes was identified in 7.7% of cases, yet these patients did not exhibit a prolonged disease course or a higher recurrence rate for LGM.** Consistent with our findings, a study on LGM patients scheduled for observation found no significant difference in the time to resolution between diabetic and non-diabetic patients (RR = 0.98, 95% CI [0.59–1.63], P = 0.94) (8). Additionally, another study investigating factors contributing to LGM recurrence did not find a significant association between diabetes and disease recurrence (OR = 1.38, 95% CI [0.59–3.25], P = 0.45) (44). While diabetes did not appear to significantly impact the disease course, careful management of glycemic control and potential interactions with immunosuppressive therapies are warranted in diabetic LGM patients. **In our study, five diabetic patients were treated with MTX, resulting in remission for four of them. One patient did not respond to treatment, and recurrence occurred in another patient, although both cases improved with conservative management.** Prior studies have also advocated for methotrexate as the preferred initial treatment for diabetic LGM patients over steroids (23).

We identified that p**atients with a subtype of LGM that is associated with EN exhibited more complex disease manifestations, including multiple breast masses and concurrent arthritis.** Additional research has also indicated that patients with concurrent LGM and EN often exhibit more extensive breast involvement (P = 0.01) (54, 55). The term GMENA (Granulomatous Mastitis, Erythema Nodosum, Arthritis) syndrome was introduced by Parperis et al. in 2021, indicating the simultaneous presence of LGM with EN and arthritis (56). Both GM and EN show similar histopathological findings with chronic inflammation and granulomas, suggesting a shared underlying cause (56). **Despite the complexity, treatment approaches involving corticosteroids and methotrexate were effective in achieving complete recovery in this subgroup of patients**. Previous studies also have suggested that individuals with LGM and EN may exhibit favorable responses to systemic immunosuppression due to shared pathophysiological mechanisms linked to autoimmunity (57, 58). For instance, one study involving 11 patients with LGM and EN treated with methylprednisolone reported full recovery within 12 weeks, with no recurrence observed during the 60-month follow-up period (59). **In our cohort, patients with LGM and EN who received either prednisone or MTX tended to have a longer disease duration compared to those without EN, although this contrast did not reach statistical significance.** However, two previous studies demonstrated a significant association between the presence of both LGM and EN and a prolonged disease course (P < 0.001, and P = 0.005) (55, 60). In our study, half of the patients with both LGM and EN had experienced a previous episode of LGM managed with prednisolone. Several studies have indicated a significantly higher recurrence rate in LGM patients with EN compared to those without EN (42.31% vs 16.00%, P < 0.001) (60,

61). However, another study found a higher recurrence rate in the EN group, but the difference was not statistically significant (16.7% vs 6.7%, P = 0.24) (55).

Our study has limitations that warrant acknowledgment. Firstly, it was conducted at a single center, potentially restricting the applicability of our findings to broader populations. However, the inclusion of a large sample size and patients with various underlying conditions may partially address these limitations. Additionally, our study recruited patients exclusively from our institution, which could introduce selection bias. This bias might result in the overrepresentation of individuals with more severe or treatment-resistant cases of LGM, potentially inflating assessments of disease severity and treatment efficacy.

CONCLUSION

In conclusion, the findings of our study highlight the complexity of managing LGM and underscore the importance of individualized treatment approaches tailored to patient characteristics and disease severity. Further research is warranted to optimize treatment strategies and improve outcomes in this challenging condition.

Our study identifies breast abscess formation as a significant characteristic associated with a prolonged disease course in patients with LGM. Clinicians should be vigilant in monitoring for signs of abscess development and employ timely interventions, if needed, to optimize patient outcomes. Further studies are warranted to explore the underlying mechanisms and clinical implications of abscess formation in LGM.

Our findings also underscore the importance of considering comorbidities in the management of LGM. Tailored treatment approaches addressing hormonal imbalances, glycemic control, and complex disease manifestations are crucial for optimizing outcomes in LGM patients with diabetes mellitus, hyperprolactinemia, and EN. Further studies exploring the mechanisms underlying these associations are warranted to inform more targeted therapeutic interventions in this complex clinical scenario.

Abbreviations

lobular granulomatous mastitis (LGM), methotrexate (MTX), interquartile range (IQR), Corticosteroids (CSs), polymerase chain reaction (PCR), angiotensin-converting enzyme (ACE), fasting blood sugar (FBS), erythrocyte sedimentation rate (ESR), erythema nodosum (EN), complete blood count (CBC), body mass index (BMI), follicle-stimulating hormone (FSH), luteinizing hormone (LH), relative risk (RR), confidence interval(CI), nuclear factor kappa-light-chain-enhancer of activated b cells (NF-kB), interleukin (IL), tumor necrosis factor (TNF), interferon (INF), Granulocyte macrophage colony stimulating factor (GM-CSF), Granulomatous Mastitis, Erythema Nodosum, Arthritis (GMENA).

Declarations

Ethics approval and consent to participate

This study was financially supported by the Mashhad University of Medical Sciences (Code: 4010734) and ethically approved by the Ethics Committee of the Mashhad University of Medical Sciences (Code: IR.MUMS.MEDICAL.REC.1401.609). All patients were included in the study with informed consent.

Consent for publication

All patients are conscious and accepting of data being published.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors report no competing interests to declare.

Funding

There was no funding.

Authors' contributions

MAR: Conceptualization. **AF**: Revising the manuscript. **FS**: Supervision, writing original draft, revising the manuscript. **SS**: Project administration. **ME**: Revising the manuscript. **MK**: Revising the manuscript. **SAA**: Revising the manuscript. **MM**: Investigation, creation of software used, analysis and interpretation of data, writing original draft of the manuscript, and project administration. All authors 1) read and approved the final manuscript and 2) have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acknowledgements

The authors express their gratitude to the patients who participated in this study and to Clinical Research Development Unit of Ghaem Hospital.

References

1. Wolfrum A, Kümmel S, Theuerkauf I, Pelz E, Reinisch M (2018) Granulomatous mastitis: a therapeutic and diagnostic challenge. Breast care 13(6):413–418
2. Farrokh D, Alamdaran A, Haddad AS, Kheirollahi M, Abbasi B (2019) Male granulomatous mastitis, a rarely encountered disorder. Breast J 25(3):517–518
3. Ucaryilmaz H, Koksal H, Emsen A, Kadoglou N, Dixon JM, Artac H (2022) The role of regulatory T and B cells in the etiopathogenesis of idiopathic granulomatous mastitis. Immunol Investig 51(2):357–367
4. Sheybani F, Naderi H, Gharib M, Sarvghad M, Mirfeizi Z (2016) Idiopathic granulomatous mastitis: Long-discussed but yet-to-be-known. Autoimmunity 49(4):236–239
5. Martinez-Ramos D, Simon-Monterde L, Suelves-Piqueres C, Queralt-Martin R, Granel-Villach L, Laguna-Sastre JM et al (2019) Idiopathic granulomatous mastitis: A systematic review of 3060 patients. Breast J 25(6):1245–1250
6. Ong SS, Xu J, Sim CK, Khng AJ, Ho PJ, Kwan PKW et al (2023) Profiling Microbial Communities in Idiopathic Granulomatous Mastitis. Int J Mol Sci 24(2):1042
7. Zeng Y, Zhang D, Zhao W, Fu N, Huang Q, Li S et al (2023) Predisposing Factors for Granulomatous Lobular Mastitis: A Case-Control Study. Int J Women's Health. :1063–1075
8. Davis J, Cocco D, Matz S, Hsu C-H, Brown MJ, Lee J et al (2019) Re-evaluating if observation continues to be the best management of idiopathic granulomatous mastitis. Surgery 166(6):1176–1180
9. Bouton ME, Jayaram L, O'Neill PJ, Hsu C-H, Komenaka IK (2015) Management of idiopathic granulomatous mastitis with observation. Am J Surg 210(2):258–262
10. Lai EC, Chan WC, Ma TK, Tang AP, Poon CS, Leong HT (2005) The role of conservative treatment in idiopathic granulomatous mastitis. Breast J 11(6):454–456
11. Azlina AF, Ariza Z, Arni T, Hisham AN (2003) Chronic granulomatous mastitis: diagnostic and therapeutic considerations. World J Surg 27:515–518
12. Yin Y, Liu X, Meng Q, Han X, Zhang H, Lv Y (2022) Idiopathic granulomatous mastitis: etiology, clinical manifestation, diagnosis and treatment. J Invest Surg 35(3):709–720
13. Postolova A, Troxell ML, Wapnir IL, Genovese MC (2020) Methotrexate in the treatment of idiopathic granulomatous mastitis. J Rhuematol 47(6):924–927
14. Di Xia F, Ly A, Smith GP (2017) Mycophenolate mofetil as a successful therapy for idiopathic granulomatous mastitis. Dermatol Online J. ;23(7)
15. Raj N, Macmillan R, Ellis I, Deighton C (2004) Rheumatologists and breasts: immunosuppressive therapy for granulomatous mastitis. Rheumatology 43(8):1055–1056
16. Godazandeh G, Shojaee L, Alizadeh-Navaei R, Hessami A (2021) Corticosteroids in idiopathic granulomatous mastitis: a systematic review and meta-analysis. Surg Today. :1–9

17. Akcan A, Öz AB, Dogan S, Akgün H, Akyüz M, Ok E et al (2014) Idiopathic granulomatous mastitis: comparison of wide local excision with or without corticosteroid therapy. Breast Care 9(2):111
18. Wang J, Zhang Y, Lu X, Xi C, Yu K, Gao R et al (2021) Idiopathic granulomatous mastitis with skin rupture: a retrospective cohort study of 200 patients who underwent surgical and nonsurgical treatment. J Invest Surg 34(7):810–815
19. Altintoprak F, Kivilcim T, Yalkin O, Uzunoglu Y, Kahyaoglu Z, Dilek ON (2015) Topical steroids are effective in the treatment of idiopathic granulomatous mastitis. World J Surg 39:2718–2723
20. Karami MY, Zangouri V, Habibagahi Z, Tahmasebi S, Ranjbar A, Seyyedy MS et al (2022) The effectiveness of local steroid injection for the treatment of breast-limited idiopathic granulomatous mastitis: A randomized controlled clinical trial study
21. Sheybani F, Sarvghad M, Naderi H, Gharib M (2015) Treatment for and clinical characteristics of granulomatous mastitis. Obstet Gynecol 125(4):801–807
22. Kafadar MT, Bahadır MV, Girgin S (2021) Low-dose methotrexate use in idiopathic granulomatous mastitis: an alternative treatment method. Breast Care 16(4):402–407
23. Kundaktepe BP, Velidedeoğlu M, Mete B (2022) The effect of methotrexate monotherapy on treatment-resistant idiopathic granulomatous mastitis patients. Surgeon 20(3):e13–e9
24. Haddad M, Sheybani F, Arian M, Gharib M (2020) Methotrexate-based regimen as initial treatment of patients with idiopathic granulomatous mastitis. Breast J 26(2):325–327
25. Aghajanzadeh M, Hassanzadeh R, Sefat SA, Alavi A, Hemmati H, Delshad MSE et al (2015) Granulomatous mastitis: presentations, diagnosis, treatment and outcome in 206 patients from the north of Iran. Breast 24(4):456–460
26. Kehribar DY, Duran TI, Polat AK, Ozgen M (2020) Effectiveness of methotrexate in idiopathic granulomatous mastitis treatment. Am J Med Sci 360(5):560–565
27. Akbulut S, Yilmaz D, Bakir S (2011) Methotrexate in the management of idiopathic granulomatous mastitis: review of 108 published cases and report of four cases. Breast J 17(6):661–668
28. Ringsted S, Friedman M (2021) A rheumatologic approach to granulomatous mastitis: A case series and review of the literature. Int J Rheum Dis 24(4):526–532
29. Ma X, Min X, Yao C (2020) Different treatments for granulomatous lobular mastitis: a systematic review and meta-analysis. Breast Care 15(1):60–66
30. Fattahi AS, Amini G, Sajedi F, Mehrad-Majd H (2023) Factors Affecting Recurrence of Idiopathic Granulomatous Mastitis: A Systematic Review. The Breast Journal. ;2023
31. Mizrakli T, Velidedeoglu M, Yemisen M, Mete B, Kilic F, Yilmaz H et al (2015) Corticosteroid treatment in the management of idiopathic granulomatous mastitis to avoid unnecessary surgery. Surg Today 45:457–465
32. Wilson JP, Massoll N, Marshall J, Foss RM, Copeland EM, Grobmyer S (2007) Idiopathic granulomatous mastitis: in search of a therapeutic paradigm. Am Surg 73(8):798–802

33. Güven HE, Pak I, Oral S (2006) Granulomatous mastitis: surgical outcomes. J Coll Physicians Surgeons–pakistan: JCPSP 16(6):431–433
34. DeHertogh DA, Rossof AH, Harris AA, Economou SG (1980) Prednisone management of granulomatous mastitis. N Engl J Med 303(14):799–800
35. Imoto S, Kitaya T, Kodama T, Hasebe T, Mukai K (1997) Idiopathic granulomatous mastitis: case report and review of the literature. Jpn J Clin Oncol 27(4):27–277
36. Asoglu O, Ozmen V, Karanlik H, Tunaci M, Cabioglu N, Igci A et al (2005) Feasibility of surgical management in patients with granulomatous mastitis. Breast J 11(2):108–114
37. Bani-Hani KE, Yaghan RJ, Matalka II, Shatnawi NJ (2004) Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. Breast J 10(4):318–322
38. Yuan Q-Q, Xiao S-Y, Farouk O, Du Y-T, Sheybani F, Tan QT et al (2022) Management of granulomatous lobular mastitis: an international multidisciplinary consensus (2021 edition). Military Med Res 9(1):20
39. Hur SM, Cho DH, Lee SK, Choi M-Y, Bae SY, Koo MY et al (2013) Experience of treatment of patients with granulomatous lobular mastitis. J Korean Surg Soc 85(1):1–6
40. Larsen LJH, Peyvandi B, Klipfel N, Grant E, Iyengar G (2009) Granulomatous lobular mastitis: imaging, diagnosis, and treatment. Am J Roentgenol 193(2):574–581
41. Pandey TS, Mackinnon JC, Bressler L, Millar A, Marcus EE, Ganschow PS (2014) Idiopathic granulomatous mastitis—a prospective study of 49 women and treatment outcomes with steroid therapy. Breast J 20(3):258–266
42. Lermi N, Ekin A, Ocak T, Bozkurt ZY, Ötegeçeli MA, Yağız B et al (2023) What predicts the recurrence in ıdiopathic granulomatous mastitis? Clin Rheumatol. :1–10
43. Tian C, Han X, Liu Z, Lv X, Ning P (2022) Management of Granulomatous Lobular Mastitis and Risk Factors Associated with Recurrence. World J Surg 46(11):2706–2714
44. Azizi A, Prasath V, Canner J, Gharib M, Sadat Fattahi A, Naser Forghani M et al (2020) Idiopathic granulomatous mastitis: Management and predictors of recurrence in 474 patients. Breast J 26(7):1358–1362
45. Huang Y, Wu H (2021) A retrospective analysis of recurrence risk factors for granulomatous lobular mastitis in 130 patients: more attention should be paied to prolactin level. Ann Palliat Med 10(3):2824–2831
46. Tan QT, Tay SP, Gudi MA, Nadkarni NV, Lim SH, Chuwa EWL (2019) Granulomatous mastitis and factors associated with recurrence: an 11-year single-centre study of 113 patients in Singapore. World J Surg 43:1737–1745
47. Nikolaev A, Blake CN, Carlson DL (2016) Association between hyperprolactinemia and granulomatous mastitis. Breast J 22(2):224–231
48. Taylor GB, Paviour SD, Musaad S, Jones WO, Holland DJ (2003) A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and

granulomatous mastitis. Pathology 35(2):109–119

49. Boutet P, Sulon J, Closset R, Detilleux J, Beckers J-F, Bureau F et al (2007) Prolactin-induced activation of nuclear factor κB in Bovine mammary epithelial cells: role in chronic mastitis. J Dairy Sci 90(1):155–164
50. Zhang L, Shi T, Yang Y, Zhang F (2014) An SLE patient with prolactinoma and recurrent granulomatous mastitis successfully treated with hydroxychloroquine and bromocriptine. Lupus 23(4):417–420
51. Ciccarelli A, Daly AF, Beckers A (2005) The epidemiology of prolactinomas. Pituitary 8:3–6
52. Seidman JD, Schnaper LA, Phillips LE (1994) Mastopathy in insulin-requiring diabetes mellitus. Hum Pathol 25(8):819–824
53. Sternberg M, Cohen-Forterre L, Peyroux J (1985) Connective tissue in diabetes mellitus: biochemical alterations of the intercellular matrix with special reference to proteoglycans, collagens and basement membranes. Diabete & Metabolisme 11(1):27–50
54. Çetin K, Sıkar HE, Güllüoğlu BM (2020) Idiopathic granulomatous mastitis with erythema nodosum: is it a variant of clinical presentation indicating treatment resistance? A retrospective cohort study. Breast J 26(9):1645–1651
55. Zheng B, Lu M, Chen C, Sun S (2023) The Distinct Pattern of Granulomatous Lobular Mastitis with Erythema Nodosum: More Severe Conditions and Extensive Lesions. J Invest Surg 36(1):2257770
56. Parperis K, Achilleos S, Costi E, Vardas M (2021) Granulomatous mastitis, erythema nodosum and arthritis syndrome: case-based review. Rheumatol Int 41:1175–1181
57. Nakamura T, Yoshioka K, Miyashita T, Ikeda K, Ogawa Y, Inoue T et al (2012) Granulomatous mastitis complicated by arthralgia and erythema nodosum successfully treated with prednisolone and methotrexate. Intern Med 51(20):2957–2960
58. Alungal J, Abdulla M, Narayan R (2016) Idiopathic granulomatous mastitis with erythema nodosum and polyarthritis. Reumatismo 68(2):97–99
59. Akin M, Karabacak H, ESENDAĞLI G, Yavuz A, Gültekin S, Dikmen K et al (2017) Coexistence of idiopathic granulomatous mastitis and erythemanodosum: successful treatment with corticosteroids. Turk J Med Sci 47(5):1590–1592
60. Luo W, Xu B, Wang L, Xiang L, Lai M, Zhang X et al (2021) Clinical characteristics and predictive factors of erythema nodosum in granulomatous lobular mastitis. Australas J Dermatol 62(3):342–346
61. Velidedeoğlu M, Papila Kundaktepe B, Mete B, Uğurlu S (2021) Idiopathic granulomatous mastitis associated with erythema nodosum may indicate a worse prognosis. Int J Rheum Dis 24(11):1370–1377

Figures

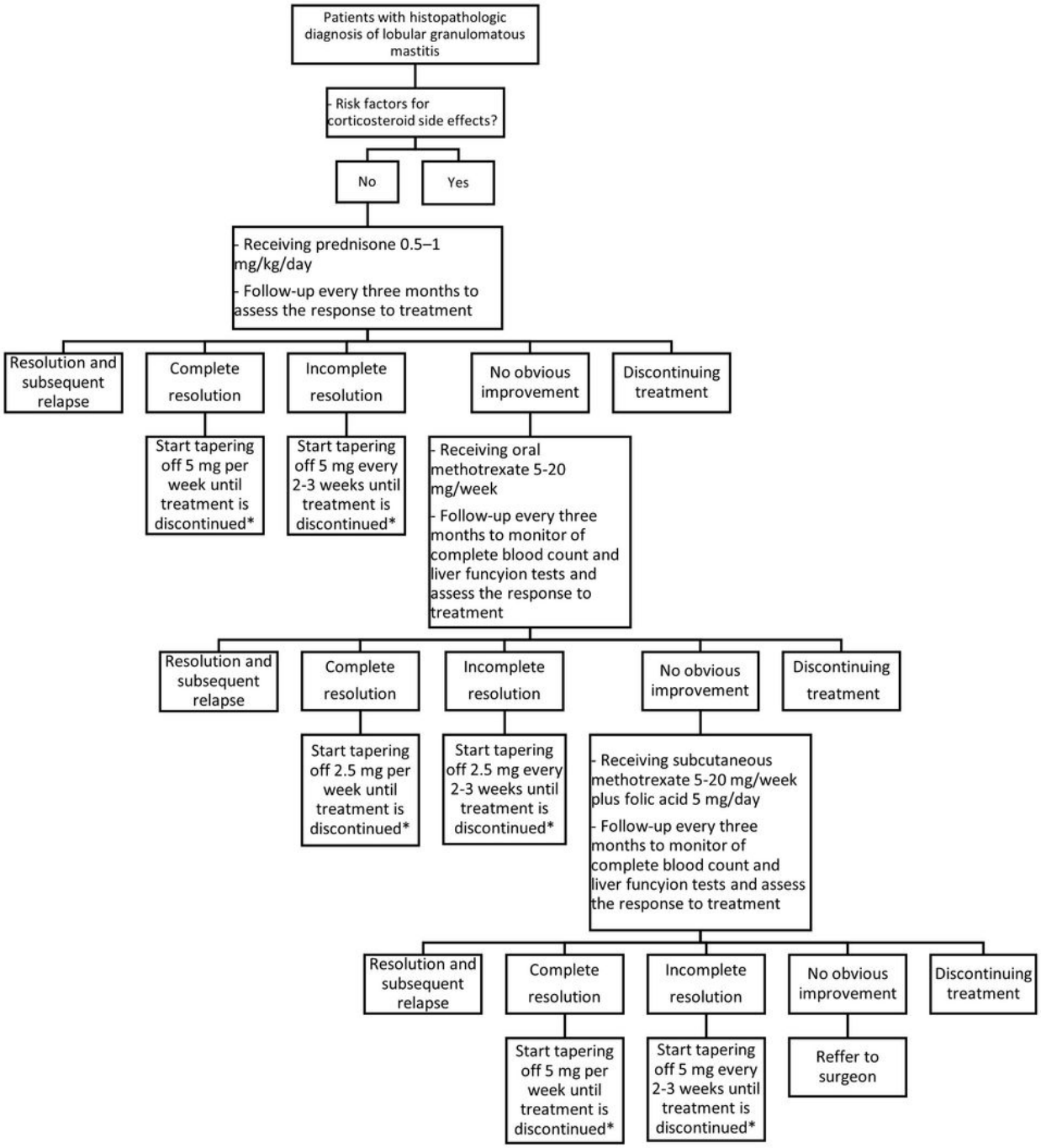

Figure 1

This figure illustrates the management of patients with LGM from the beginning of the study until the complete resolution of symptoms