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The Cure for Idiopathic Granulomatous Mastitis without Surgery and Steroids: One Size Does Not Fit All

İdiopatik Granülomatöz Mastitin Ameliyatsız ve Steroidsiz Tedavisi: Tek Beden Herkese Olmaz

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ABSTRACT

Aim: Idiopathic granulomatous mastitis (IGM) is a rare inflammatory breast disease mimicking malignancy with no consensus on the optimal treatment. We aimed to present a single-center algorithm for IGM treatment without surgery and steroids.

Material and Methods: This study was conducted between 2010 and 2020. A prospective database was reviewed to identify patients with biopsy-proven IGM who were managed through observation and ultrasound-guided interventions over a 10-year period.

Results: Seventy-eight female patients with a confirmed diagnosis of IGM via reevaluation were determined. Of these, 34.61% required ultrasound-guided abscess aspiration and 10.25% required incisional abscess drainage without surgical resection. Complete clinical resolution was achieved within 6 months in 58.97% cases. The overall recurrence rate was 12.82%, and surgical drainage was required in one patient. Univariate logistic regression analysis revealed no statistically significant association between recurrence and the demographic or pathologic factors evaluated. Twenty-two (28.2%) patients with a histopathologic diagnosis of cystic İGM who received antibiotics (doxycycline) achieved complete resolution within 2 weeks and experienced no recurrence.

Conclusion: IGM is a self-limiting disease that resolves spontaneously independent of medical intervention and without resection in up to 18 months. After diagnosis, surgery with or without steroids as the first line of therapy should be replaced with close observation and ultrasound-guided interventions according to patients' preferences.

Keywords: Granulomatous mastitis, observation, steroid, surgery, treatment

ÖZ

Amaç: İdiyopatik granülomatöz mastit (IGM), optimal tedavi konusunda fikir birliğine varılamayan, maligniteyi taklit eden nadir görülen inflamatuar meme hastalığıdır. IGM olguları için cerrahi müdahale yapılmadan ve steroid tedavisi verilmeksizin tedavileri için tek merkezli bir algoritma sunmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma, 2010-2020 yılları arasında gerçekleştirildi. 10 yıllık bir süre boyunca klinik gözlem ve ultrason eşliğinde müdahalelerle tedavi edilen, biyopsi ile kanıtlanmış IGM' li hastaları belirlemek için prospektif veri tabanı gözden geçirildi.

Bulgular: IGM tanısı doğrulanan 78 kadın hasta belirlendi. Bunların %34,61' inde ultrason eşliğinde abse aspirasyonu ve %10,25' inde cerrahi rezeksiyon olmadan insizyonel apse drenajı gerekti. Vakaların %58,97' sinde 6 ay içinde tam klinik iyileşme sağlandı. Genel nüks oranı %12,82 iken bir hastada cerrahi drenaj gerekti. Tek değişkenli lojistik regresyon analizi, demografik veya patolojik faktörler arasında istatistiksel olarak anlamlı bir ilişki olmadığını ortaya çıkardı. Histopatolojik olarak kistik IGM tanısı alan ve antibiyotik (doksisiklin) alan 22 (%28,2) hastada 2 hafta içinde tam iyileşme sağlandı ve nüks görülmedi.

Sonuç: IGM, tıbbi müdahaleden bağımsız olarak ve rezeksiyona gerek kalmadan 18 aya kadar sürede kendiliğinden düzelen, kendi kendini sınırlayan bir hastalıktır. Tanı konulduktan sonra tedavinin ilk basamağı olan steroidli veya steroidsiz cerrahinin yerini hastanın tercihine göre yakın gözlem ve ultrason eşliğinde müdahaleler almalıdır.

Anahtar Sözcükler: Granülomatöz mastit, gözlem, steroid, cerrahi, tedavi

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, chronic disease of the breast first described in 1972 (1). Histopathologically, IGM is characterized by chronic non-necrotizing lobulocentric granulomatous inflammation around lobules and ducts with a prolonged recurrent disease course (2). IGM has a diverse clinical presentation with a large spectrum of symptoms ranging from a painful breast mass to breast abscess with skin ulcerations and tract formations (3). Until now, an evidence-based specific etiology and a definitive treatment have not been established, but previous studies focused on several factors hypothesizing the importance of autoimmune, infectious, or hormonal causes (4,5). IGM is most commonly a disease affecting young women of reproductive age with a greater incidence in Middle East and Asia, suggesting a common environmental and probably a genetic etiology for this benign disease (6). The self-limiting clinical course in some cases managed with observation alone suggests that autoimmunity is likely the pivotal factor in the etiology and mechanism of the disease process. An association between the histologic pattern defined as cystic neutrophilic granulomatous mastitis and *Corynebacterium kroppenstedtii* infection has also been reported (7). Accordingly, IGM seems to be a heterogenous group of diseases with various etiologies and clinical courses. Therefore, the management algorithm should be designed considering patient factors and clinical presentation.

There are major issues regarding the diagnosis and treatment of IGM with devastating outcomes in cases of recurrence. The definitive medical and surgical treatment is a great challenge to patients and surgeons, which results in serious consequences regarding quality of life and breast cosmesis. IGM is not associated with an increased risk of subsequent breast carcinoma. However, one of the main issues to be addressed is making an accurate diagnosis for IGM. Moreover, differentiation from an overlooked cancer and avoiding unnecessary mastectomies are essential (8).

There is no consensus regarding the optimal treatment of IGM (9). The disease is still considered as idiopathic because of its undefined etiology and elusive clinical course. There has been a paradigm shift in the treatment from extensive surgical interventions including mastectomy to more conservative medical treatment approaches including antibiotics, anti-inflammatory drugs, and corticosteroids. Moreover, observation alone has been proposed as the best management for this benign self-limiting disease with flares and alleviations (10).

The difficulty regarding definitive treatment and ongoing recurrences is associated with prolonged courses of antibiotics and steroids, and extensive surgical procedures. Due to the fact that IGM is a benign disease without life-threatening consequences, before initiating any management or treatment, especially those that cause permanent damage to breast or have potential side effects, a serious case-by-case individualized assessment should be performed. Herein, we report the 10-year experience of observation and image-guided interventions for IGM management in an academic facility. This study was conducted to evaluate a large series of IGM patients with a long period of follow-up, managed with close observation and ultrasound-guided interventions but without steroids and extensive surgery. A proposed algorithm for individualized management with a discussion of its rationale in terms of pathologic evaluation and minimally invasive interventions is presented.

MATERIAL and METHODS

Data Acquisition

A retrospective graphical review of our database, prospectively maintained at Bulent Ecevit University, Obesity and Diabetes Practice and Research Center, Clinic of General Surgery, was conducted to identify patients with biopsy-proven IGM, managed through observation and ultrasound-guided interventions, but without steroids over a 10-year period (between 2010-2020, total 133 patients). The university ethics council approved this study (Institution review board number: 2021/13). Each patient's data was reviewed for demographics, including age, reproductive history, disease presentation, treatments, and clinical course, and personal and medical history of tuberculosis, sarcoidosis, and autoimmune disease. Results of laboratory and radiologic work-up including tissue cultures, chest radiograph, mammogram, breast ultrasonography, and biopsy results were extracted. Ultrasound-guided interventions, perioperative records (if performed), and medications used were reviewed.

Pathologic Evaluation

An experienced breast pathologist reviewed all cases and confirmed the diagnosis of GM in 78 of 133 mastitis cases from pathology archives of hematoxylin-eosin-stained slides. The demographic and pathologic data of 55 confirmed nongranulomatous mastitis cases were compared with granulomatous mastitis cases for recurrence. The examination was based on light microscopy morphological findings. The study included cases with non-neoplastic lesions and accompanying lesions. The presence of non-caseating inflammatory granulomas within lobules containing lymphocytes, plasma cells, eosinophils, epithelioid histiocytes, and multinucleated giant cells was used to make the diagnosis of IGM. Histopathologic analysis was reviewed and graded based on pathognomonic features for cystic IGM, such as microabscess formation, fibrosis, and inflammatory cell intensity. The presence of typical granuloma formation led to this diagnosis. A granuloma was made up of syncytial epithelioid histiocytes with large cytoplasm and multinuclear giant cells formed by the fusion of these histiocytes and lymphocytes or other inflammatory cells in their surroundings. The inflammatory cells that accompanied the granuloma formation differed as well (Figure 1A-D). Acid-fast bacilli (AFB stain) and fungal organisms (Grocott-Gomori methenamine silver-GMS stain) were stained separately. Granulomatous inflammation is common in some infections, particularly those caused by mycobacteria, fungi, or parasites, as well as in reactions to foreign bodies or ductal ectasia. Granulomatous inflammations, particularly those caused by mycobacteria, are characterized by necrosis in the granuloma's center. Because of its macroscopic appearance, this necrosis is known as caseification necrosis. Necrosis may occur in a coagulation pattern in some infectious diseases. The cases with granuloma formation were divided into two groups based on the presence or absence of necrosis (caseification and coagulation). The presence of an enlarged duct structure with secretion and foamy histiocytes in its lumen was used to diagnose ductal ectasia. Mastitis with granulomas has also been defined in relation to Corynebacterium infection. Mastitis was distinguished by the presence of non-necrotic granulomas and oval cystic cavities surrounded by neutrophils. These cavities were actually lipid vacuoles. The cases were classified based on the presence or absence of these cystic cavities. Gram histochemical staining revealed the presence of gram-positive bacilli in the cystic cavities, confirming the presence of the infectious agent. The density of inflammatory cells, such as neutrophils, eosinophils, epithelioid histiocytes, lymphocytes, plasma cells, and giant cells, was graded using a 4-point scoring system. The scoring system used by Grigoriadi et al. for tumor-infiltrating lymphocytes in

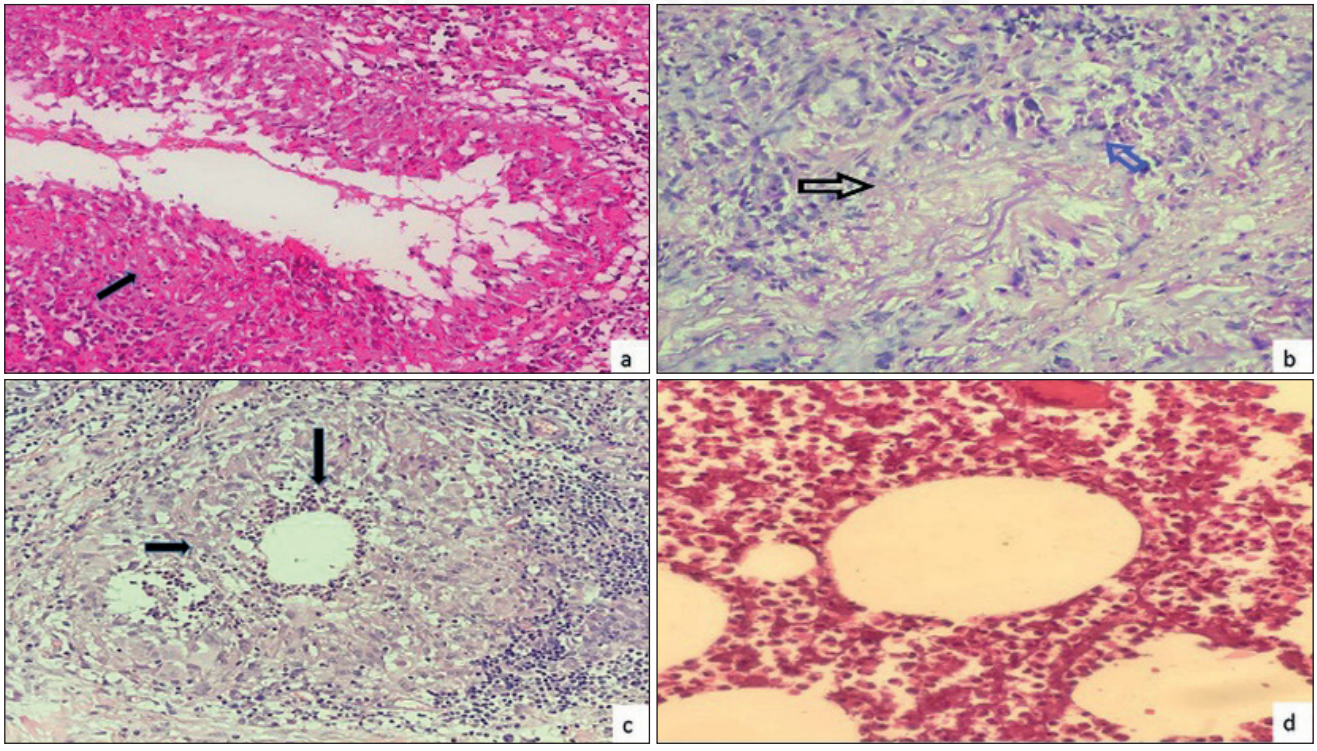

Figure 1: A) A granuloma formation with epithelioid histiocytes in a syncytial pattern (HEx20), **B)** A small granuloma formation with caseification necrosis (HEx20), **C)** Oval cystic cavities surrounding neutrophils and epithelioid histiocytes (HEx10), **D)** Cystic granulomatous neutrophilic mastitis with HEx400.

breast cancer patients was used as the basis for this scoring (11). Accordingly, the absence of cells was graded 0 for each inflammatory cell; 1%-10% for grade 1 (minimal); 10%-20% for grade 2 (mild); 20%-50% for grade 3 (moderate); and more than 50% for grade 4 (strong) (Figure 2A-C). In mastitis cases with a high concentration of neutrophilic cells, neutrophils can form small groups known as microabscesses, which were divided into two groups based on the presence or absence of these microabscesses in the presented series (Figure 3A-F). Inflammation consisting of histiocytes, giant cells, and neutrophils in the adipose tissue surrounding the breast parenchyma, known as fat necrosis,

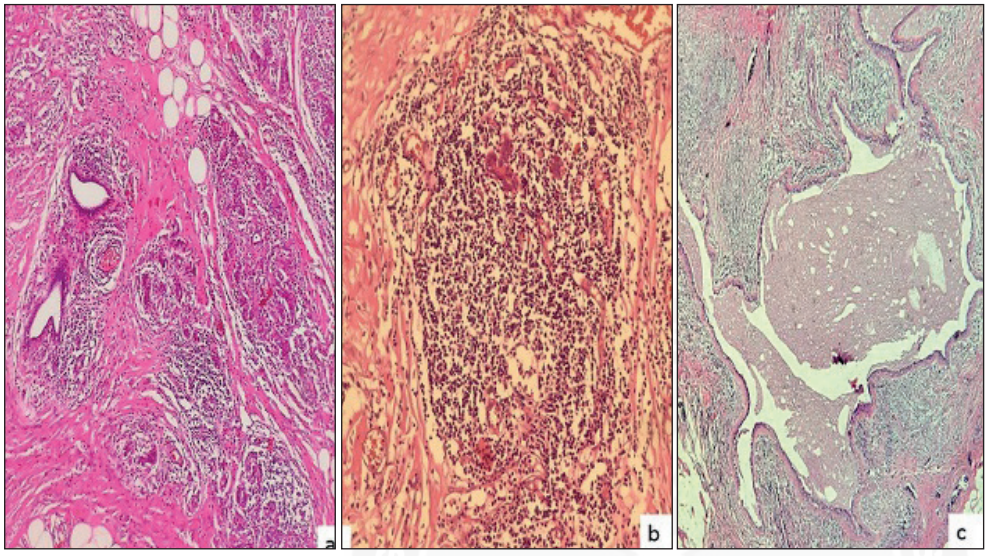

Figure 2: Distrubition pattern of inflammation. **A)** Periseptal inflammation (HEx40), **B)**. Lobulocentric pattern of inflammation (HEx100), **C)** Periductal inflammation with ductal ectasia (HEx40).

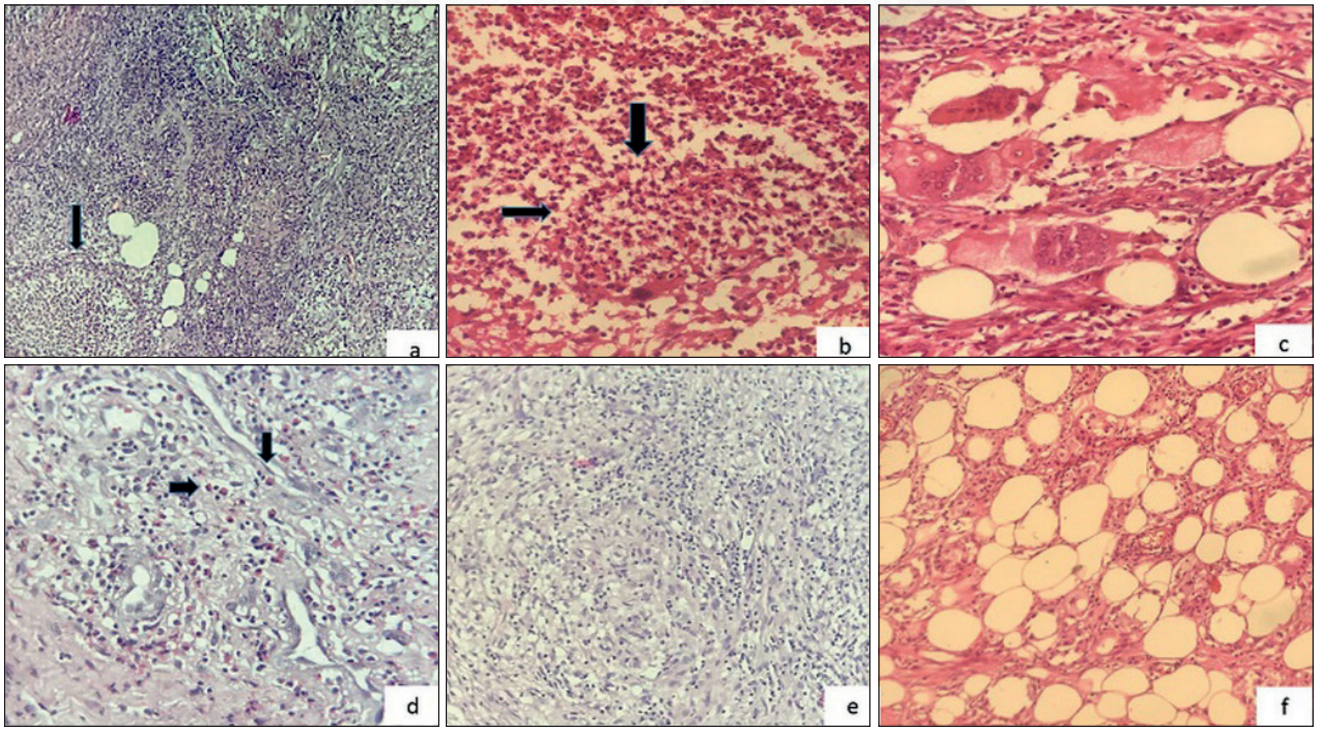

Figure 3: Different patterns of mastitis. **A)** Neutrophilic mastitis with microabscess (with arrow) (HEx40), **B)** Microabscess marked with arrow (HEx200), **C)** inflammation rich in mulitnuclear giant cells (grade 3) (HEx400), **D)** Eosinophilic mastitis (HEx200), **E)** Lobulocentric inflammation with dense lymphocytes (HEx200), **F)** Mastitis with fat necrosis (HEx100).

was evaluated. Vasculitis was diagnosed when neutrophils infiltrated the wall of small vascular structures in the breast parenchyma and fibrin accumulated in the wall. In addition, fibrosis was evaluated using the semiquantitative scoring system proposed by Van den Eynden et al (12). to evaluate fibrotic foci. The absence of fibrosis was grade 0, mild fibrosis grade 1, moderate fibrosis grade 2, and severe fibrosis grade 3.

Patients and Management Algorithm

A retrospective chart review was completed, which included demographic characteristics, clinical presentation, clinical management, and outcomes. The management strategy included close observation with supportive care, and when necessary, ultrasound-guided aspiration of the abscess and irrigation with saline. Incisional drainage was the procedure of choice for cases that were resistant to irrigation due to necrosis and antibiotics. However, no extensive surgical excision was performed. All patients diagnosed with IGM were informed about their disease in detail by an experienced breast surgeon, and the management strategy was discussed with each patient, according to our institutional algorithm. Patients were assured that the disease is benign, has a varied clinical course characterized by episodes, and will resolve spontaneously without the use of medications. However, patients must be patient, as this process could take up to 2 yr, and the disease may worsen more than once before it resolves due to the nature of the condition. Patients were also reassured that the surgeon will examine them on a regular basis and intervene through ultrasound-guided procedures or surgery as needed. The patient's satisfaction and trust in the physician are of the utmost importance. During any observation period or during the disease course, none of the patients presented received corticosteroids. When no persistent lump, induration, or skin fistula/wound was observed, patients were considered to have achieved complete resolution. Each patient's time to resolution, number of image-guided interventions, need for surgical drainage, and recurrences were evaluated.

Statistical Analysis

All continuous variables were expressed as mean with range and categorical variables as frequency with the respective proportion in percentage. Nominal and ordinal variables were described by frequency analysis, and scale variables as mean and standard deviations. Kolmogorov-Smirnov test was used to assess normality for scale parameters. Since all scale variables were non-normally distributed, Mann-Whitney U test was used to compare differences in scale variables. Ordinal or nominal variable differences were analyzed using Chi-Square test and Chi-Square Likelihood Ratio. Spearman's rho correlation analysis was used to evaluate the relationship between research variables. Binary logistic regression was used to analyze the risk factors associated with recurrence, and *p*-value of <0.050 was considered significant. SPSS 17.0 for windows was used for analysis at 95% confidence interval with 0.05 significance level.

RESULTS

Demographics

A total 78 female patients with the diagnosis of IGM were evaluated. Table 1 summarizes the sociodemographic characteristics of the patients. The median age of onset was 34 years (range 23-67 years). Seventy-six (97.43%) patients were parous, and none of them was pregnant. A history of lactation was within 6 months prior to diagnosis in seven (8.97%) patients. Six patients were active and 10 patients were former smokers. Hyperprolactinemia was present in 14 patients (17.94%) at the time of diagnosis.

Clinical and Radiographic Presentations

The clinical characteristics, radiological features, culture results, radiologic evaluation, and treatment and follow-up data are summarized in Table 2. The average duration of symptoms was 0.3 months (0.1weeks to 3 months). The most common presenting symptom was a palpable breast lump in 70 patients (89.74%), followed by pain, skin chang-

Table 1. Sociodemographic characteristics

	Patients N = 78, n (%)
Median age in years (range)	34 (23-67)
Median menarche in years (range)	13 (11-16)
Median number of pregnancies (range)	2 (0-5)
Mean age of first live birth (range)	24.16(17-37)
Smoking status	
Former	10 (12.82)
Current	6 (7.69)
Never	62 (79.48)
Mean body mass index, (kg/m^2) (range)	31.48 (23-42)
Diabetes mellitus	
Yes	6 (7.69)
No	72 (92.3)
Prolactin level	
High	14 (17.94)
Normal	64 (82.05)
Education	
Elementary	25 (32.05)
Middle School	22 (28.2)
High School	23 (29.48)
College	8 (10.25)

es (erythema, warmth, and thickening), and induration in 65 patients (83.33%). Forty-seven patients presented with a painful breast lump (60.25%). Other presenting symptoms included fistula formation and breast abscess. Sixty-two patients (79.48%) had multifocal disease.

Table 2. Clinical characteristics, presentation, radiologic evaluation, and outcome of patients with idiopathic granulomatous mastitis

	Patients, n (%)
Duration of symptoms at presentation, months (range)	0.3 (0.1-3)
Clinical presentation	
Palpable mass	70 (89.74)
Mean size of mass, mm. (range)	29.94 (11-80)
Pain	47 (60.25)
Erythema	46 (58.97)
Induration	65 (83.33)
Skin tracts and/or drainage	10 (12.82)
Nipple inversion	45 (57.69)
Abscess	44 (5.41)
Imaging evaluation	
US	78 (100)
MMG	44 (56.41)
BIRADS 0	5 (6.41)
BIRADS 1	0 (0)
BIRADS 2	3 (3.84)
BIRADS 3	15 (19.23)
BIRADS 4	40 (51.28)
BIRADS 5	10 (12.82)
Not reported	6 (7.69)
Microbiology findings	
Culture negative	61 (78.20)
Culture positive	17 (21.79)
Corynobacterium	5 (6.41)
Other	12 (12.82)
Treatment	
Antibiotics	40 (51.28)
US guided aspiration and irrigation	27 (34.61)
Incisional drainage	8 (10.25)
Surgical intervention	4 (5.12)
Time to resolve with observation Mean time to resolution	
1-6 months	46 (58.9)
7-11 months	17 (21.79)
>12 months	11 (14.1)
Recurrence	10 (12.82)

Chest radiography was normal in all patients. All patients had breast ultrasound at the time of admission. Forty-four patients (56.41%) had performed both mammography and breast ultrasound at presentation. Office-based ultrasound was performed to each patient by the surgeon at the time of diagnosis, and the sonographic appearance was categorized into benign lesions reminiscent of abscesses and suspicious features suggesting a carcinoma. Of these patients, 40 (51.28%) were classified as having a breast imaging reporting and data system (BIRADS) of 4, and 10 (12.82%) were classified as BIRADS 5. The most common sonographic definition was heterogeneous, ill-defined mass-like areas including phlegmonous changes, increased density, and diverse amounts of fluid collections presented multifocally. Mammographic evaluation showed focal asymmetry, skin thickening, scattered densities, and obscure masses.

Pathologic and Microbiologic Findings

Histological diagnosis was established via ultrasound-guided core needle biopsy in the first attempt in 80 (95%) cases, and five patients required a second attempt. Bacterial cultures were performed in all patients. Seventeen patients (21.79%) had positive bacterial culture results of which Corynebacterium was isolated in 5 (29.41%) cases. Tissue stains for acid-fast bacilli and fungi were performed on all cases and returned to be negative. Forty (51.28%) patients received antibiotics. In 22 patients (28.2%) with histopathologic diagnosis of cystic granulomatous mastitis, doxycycline (100 mg orally twice daily) was the preferred choice regardless of isolating Corynebacterium in the culture medium, all of whom responded completely within 2 weeks and experienced no recurrence within a mean follow-up period of 32 months (1-5 years). Non-steroidal anti-inflammatory drugs were prescribed to be used when necessary.

Histopathologic reevaluation identified necrosis and microabsess in 14 (17.94%) and 47 (60.25%) cases, respectively. Mild to moderate fibrosis was seen in 20 (25.64%) patients. Inflammatory cell grading revealed grade 3-4 presence of polymorphonuclear leucocytes (PMNL), epithelioid histiocytes, lymphocytes, plasma cells, and giant cells in 53 (67.94%), 28 (35.89%), 14 (17.94%), 14 (17.94%), and 10 (12.82%) of patients, respectively. Fat necrosis and vasculitis were not found in any case.

Management and Outcome Data

All 78 patients received observation without steroids. Twenty-seven (34.61%) patients required ultrasound-guided abscess aspiration and irrigation, which was performed once in 15 patients, twice in 6 patients, and three times in 6 patients. Ten (12.82%) patients had draining fistulas on the skin at the time of diagnosis, which resolved between 3 to 10 months. A total of 8 (10.25%) patients required incisional abscess drainage without surgical resection, three of whom had fistulas.

Complete clinical resolution (CCR) was achieved in 46 (58.97%) patients within 6 months, 17 (21.79%) patients in 1 year, and 11 (14.1%) patients required more than one year. The median time for resolution was 5 months, ranging from 2 weeks to 24 months. CCR was achieved in more than 1 year in patients who had multifocal abscess at presentation, had more than one fistula on the skin, and were resistant to ultrasound-guided irrigations. Only 4 (5.12%) patients required surgical intervention during the follow-up period.

Ten patients who had spontaneous clinical and radiological resolution developed recurrence (12.82%). Of these, 6 patients were treated with antibiotics only, 3 patients required image-guided intervention, and surgical drainage was employed in one patient. The mean time from resolution to recurrence was 15 months (range: 9 months-3 years). Only 3 patients experienced more than one recurrence, which required neither antibiotics nor surgical drainage and was managed conservatively within 2 months. Univariate logistic regression analysis revealed no statistically significant association between recurrence and the demographic and pathologic factors evaluated (Table 3).

Table 3. Univariate logistic regression analysis for recurrence

	Univariate	
	OR (%95 CI)	**p**
Age	1.014 (0.954-1.078)	0.652
Age of menarche	1.837 (0.857-3.938)	0.118
Number of gestations	0.536 (0.26-1.102)	0.090
Age of first live birth	1.038 (0.911-1.183)	0.576
Body mass index (kg/m^2)	1.039 (0.904-1.195)	0.587
Prolactin level (n)	1.167 (0.22-6.199)	0.856
Duration of symptoms	0.949 (0.87-1.034)	0.231
Palpable mass	0.675 (0.169-2.689)	0.577
Size of mass (mm)	1.005 (0.958-1.055)	0.828
Pain	2.974 (0.587-15.064)	0.188
Erythema	3.158 (0.624-15.985)	0.165
Abscess	3.556 (0.703-17.985)	0.125
Culture result	1.608 (0.402-6.428)	0.502
Antibiotics	2.029 (0.376-10.949)	0.411
Fibrosis	1.355 (0.462-3.98)	0.580
Necrosis	1.167 (0.22-6.199)	0.856
Microabscess	1.633 (0.388-6.867)	0.503
PMNL	0.788 (0.424-1.465)	0.451
Eosinophils	1.324 (0.558-3.143)	0.524
Epithelioid histiocytes	0.949 (0.47-1.915)	0.883
Lymphocytes	1.417 (0.53-3.765)	0.485
Plasma cells	0.58 (0.204-1.649)	0.307
Giant cells	1.037 (0.515-2.085)	0.920

A comparison regarding baseline characteristics and outcomes of patients with granulomatous and non-granulomatous mastitis (78/55) revealed that age, ductal ectasia rate, lymphocyte and plasma cell parameters were significantly higher in the non-granulomatous group, whereas microabscess rate, PMNL and giant cell parameters were significantly higher in the patients with granulomatous mastitis ($p < 0.05$) (Table 4). Localization was higher in the lobulocentric site in the granulomatous mastitis group and in the periductal site in the non-granulomatous group, with a significant difference, and recurrence was found to be significantly higher in granulomatous mastitis, as expected ($p < 0.05$). Correlation analysis results showed that age, localization, ductal ectasia, associated breast lesion, lymphocyte and plasma cell presence was negatively correlated with granuloma ($p < 0.01$). On the contrary, microabscess, PMNL, and giant cell parameters were positively correlated with granuloma ($p < 0.01$).

DISCUSSION

Currently, the lack of consensus on the most effective and the least harmful treatment strategy for IGM provides a basis for optimizing management considering individualized factors and expectations. Accordingly, there cannot be one right choice, and the selection should be made regarding specific factors in a case-by case manner. Most of the patients would benefit greatly from observation and image-guided minimal invasive procedures while avoiding the risks of adverse side effects due to steroids or poor cosmetic outcome due to extensive surgical resections. However, in some patients, the time to resolution would be unacceptable, or recurrences would be inevitable, which we have been able to manage conservatively. Some patients would experience several recurrences or a longer resolution time, which might be unacceptable to them (13). As recommended in the literature, before selecting the observation choice, it is rational to use a shared decision-making approach with the patients after discussing the possible clinical scenarios they might experience (13,14). Since the resolution time varies with observation, shorter resolution periods with steroid applications or surgery should be shared with the patients together with possible side effects (10,15,16).

With the well-documented low incidence and lack of evidence-based treatment algorithms, IGM patients are prone to be exposed to various treatments by different clinicians globally (16). In the past, extensive surgeries were a common approach with a reported rate of resolution not exceeding 75% in most series and leading to poor cosmetic outcome (17-19). Moreover, historically mastectomy has been employed in some unfortunate cases, which is extreme and completely out of the scope of the current era, which recommends breast conservation even in malignant

Table 4. The comparison of baseline characteristics and outcomes for patients with granulomatous and non-granulomatous mastitis

	Non- granulomatous (n = 55)	Granulomatous (n = 78)	p
Age, mean ± SD	44.38 ± 11.22	36.56 ± 10.20	0.000[a]
Localization, n (%)			
Lobulocentric	-	66 (88.0)	
Periductal	39 (67.2)	-	0.000[b]
Lobulocentric + Periductal	-	9 (12.0)	
Interlobular	17 (29.3)	-	
Interlobular + Periductal	2 (3.4)	-	
CGNM, n (%)	-	22 (29.3)	
Ductal ectasia, n (%)	18 (31.0)	1 (1.3)	0.000[c]
Necrosis, n (%)	-	14 (18.7)	
Microabscess, n (%)	16 (27.6)	47 (62.7)	0.000[c]
Fat necrosis, n (%)	6 (10.3)	-	
Vasculitis, n (%)	-	1 (1.3)	
Comorbid breast lesion, n (%)			
None	42 (72.4)	70 (93.3)	
Fibrocystic change	14 (24.1)	1 (1.3)	
Ductal epithelial hyperplasia	1 (1.7)	3 (4.0)	0.000[b]
Fibroadenoma	-	1 (1.3)	
Foreign body interaction	1 (1.7)	-	
Recurrence, n (%)	0 (0)	10 (13.3)	p < 0.05
Fibrosis, mean ± SD	0.43 ± 0.84	0.31 ± 0.57	0.831[a]
PMNL, mean ± SD	1.77 ± 0.79	2.87 ± 1.04	0.000[a]
Eosinophils, mean ± SD	0.91 ± 0.63	1.17 ± 0.72	0.053[a]
Epithelioid, mean ± SD	-	2.23 ± 0.86	
Lymphocyte, mean ± SD	2.91 ± 0.73	1.92 ± 0.65	0.000[a]
Plasma cell, mean ± SD	3.14 ± 0.85	1.49 ± 0.76	0.000[a]
Giant cell, mean ± SD	0.09 ± 0.34	1.43 ± 0.93	0.000[a]

a. Mann-Whitney U Test, b. Chi-Square Likelihood Ratio, c. Chi-Square Test

disease (8,20). Since observation and medical treatments have a significant impact on improved outcomes, surgery should only be reserved for patients with resistant disease to other conservative management modalities. In our series, 45% of the cases had mastitis involving the whole quadrant of the breast. Surgical resection would probably lead to some degree of esthetic deformity that could impair the quality of life of these young patients. Similarly, Shin et al. reported that wide local excisions resulted in higher recurrence rates with permanent extensive scarring (18). The recurrence even after mastectomy shed some valuable light on the pathogenesis of the disease, supporting that the cure rate does not improve with larger excision.

One of the major issues about IGM is the CCR and recurrence rates. In a literature review, complete resolution rate and recurrence rate for oral steroids, oral steroids plus surgical management, and topical steroids were reported to be 71.8% and 94.5%, 98.8% and 20.9%, and 4% and 14%, respectively, supporting the conclusion that surgery plus steroids would be a rational choice (13). However, concerns about surgery such as stress, scars, and poor cosmetic outcome lead patients to seek more conservative treatment options. In this review, the complete remission rate was 95% for observation alone with a recurrence rate of 12.82%, which was managed via conservative measures. Hence, topical steroids and observation are viable options that should be offered to patients (13). The median clinical resolution time of 5 months and lower recurrence rate with attenuated episodes resolving in 2 months without major interventions such as surgery and steroids in our series merits consideration. In the current study, analysis of the factors that were considered to have possible effects on

time to resolution and recurrence revealed no significant finding, which might be attributed to the lower number of recurrent cases.

An interesting finding in our study was that 22 patients with cystic GM received antibiotics in the form of doxycycline, which was irrelevant to the isolation of a Corynebacterium species. All these patients had complete resolution within 4 weeks and experienced no recurrence. Similarly, Brownson et al. reported no recurrence in three cases of cystic GM without recurrence and concluded that histopathologic identification of cystic GM could result in a therapeutic paradigm shift toward treatment solely with an extended course of antibiotics targeting Corynebacterium (21). In accordance with our data, this finding supports the hypothesis that infection may be the etiologic factor in a subgroup of IGM patients. Even if the tissue cultures are negative, targeted antibiotic treatment to Corynebacterium species for patients with confirmed cystic GM would cure IGM without recurrences. On the other hand, Tang et al. reported recurrent disease in only 4 of 17 patients with positive culture results for Corynebacterium and concluded based on univariate analysis that this infection led to 2.64 times increased risk of developing recurrence (15). However, multivariate analysis is lacking in their series, and none of our patients experienced recurrence. Hence, meticulous pathologic analysis and reporting would decrease unnecessary antibiotic use and would serve to guide physicians in the decision to prescribe antibiotics (22). A meta-analysis by Martines-Ramoz et al. evaluating 3060 patients with IGM found that antibiotics were used in up to 88% of cases and were the most frequent treatment in underdeveloped countries (23). Beyond providing cost-effectiveness, rational antibiotic prescription would serve to prevent resistance to these drugs, which is a global phenomenon currently. In the presented series, antibiotic prescription was performed regarding culture results and abscess presence according to our institutional regulations.

The present study has some limitations including its retrospective design and sample size. Nevertheless, the data was obtained from a prospectively recorded database in an academic center with an institutional management algorithm for IGM. All of the analyzed patients were informed and followed-up by an experienced breast surgeon and examined via sonography in an outpatient clinic at each visit according to the protocol. As the accurate etiologic agents in the pathogenesis of IGM such as hormones, immunoglobulins, and ethnicity need to be determined via further prospective trials, which seems unlikely to be performed due to resource constraints, the success rate of observation without steroids and extensive surgery merits consideration, particularly for underdeveloped countries with higher disease incidences and limited financial resources. Other factors such as infection play a major role in a subgroup of patients with CCR in a shorter period of time and without recurrence. The mindfulness of the physician and the compliance of the patient to the recommended treatment is of paramount importance.

The present study demonstrated that IGM is a self-limiting disease that resolves spontaneously irrespective of the treatment received within a variable period ranging from 2 months to 18 months. However, the recurrent nature is a fact, and the episodes can occur at any time interval and could be managed conservatively as well. The major issue is to inform and reassure the patient that complete resolution might last longer and that even recurrence is not unpredictable. The confidence between the patient and the physician would prevent surgical interventions causing breast deformity and unnecessary medications such as steroids or antibiotics with potential side effects. Taken together, all these factors are associated with cost-effectiveness, resource management, and improved quality of life regarding cosmetic issues.

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Conflicts of Interest

No conflict of interest is reported by authors.

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Ethical Approval

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