Clinical, microbiological, immunological and hormonal profiles of patients with granulomatous mastitis

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Abstract. Various studies on the etiology and other aspects of granulomatous mastitis (GM) have been performed; however, a lot of controversies have arisen. The present study aimed to present the clinicopathological findings and identify the sensitivity and resistance of isolated bacteria in patients with GM. In this cross-sectional study 63 female patients with a confirmed histopathological diagnosis of GM were included. A core needle biopsy was conducted for the patients to obtain a sample for histopathological examination and bacterial culture. In total, 46 types of antibiotics were used to determine the sensitivity and resistance of each isolated bacterial species. All the medical and clinical records of the patients were acquired through the completion of a questionnaire form in person or, if necessary, through the evaluation of their medical records in the database of the relevant center. The majority of the patients were in the premenopausal or perimenopausal period. GM was unilateral in 58.7% of the patients. The most common symptom was pain, followed by fever and chills. The mean ranges of the erythrocyte sedimentation rate, C-reactive protein, IL-6, IL-17, C5a, white blood count, neutrophil-to-lymphocyte ratio, and prolactin tests were significantly elevated in comparison to the normal ranges. In total, nine different bacterial species were isolated from the bacterial culture of the core biopsy samples, and 50% of the isolated bacterial species were sensitive to trimethoprim-sulfamethoxazole. Since there is no consensus on the etiology of GM, any additional studies related to this aspect expand the current understanding of this puzzling condition.

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Introduction

Granulomatous mastitis (GM) is a benign inflammatory disease of the breast that was first reported in 1972 (1). This rare entity commonly affects female patients during their reproductive period. It is associated with an ill-defined etiology (2,3). GM is generally characterized by a non-caseating granulomatous inflammation in close proximity to the ducts and lobules of the breast (2). The granulomas are usually unilateral and appear as a solid mass in the upper outer quadrant of the breast (4). Several clinical findings, including palpable masses, fistulae, nipple retraction, breast skin inflammation, ulcers, and abscess formation have been associated with GM (5,6). The major etiology of GM remains controversial, which may lead to misdiagnosis and complicate treatment (7). Some factors like heredity, bacterial infection, fungal infection, use of contraceptive drugs, high levels of prolactin, alpha-1 antitrypsin deficiency, and smoking have been suggested to cause GM. In addition, triggering autoimmune reactions due to the presence of milk proteins in the interstitial breast tissues is regarded as a favorable hypothesis concerning the occurrence of GM (2,8). With regard to the clinicopathological and radiological findings, GM can mimic and easily be mistaken for breast cancer and other pathologies, including tuberculosis, mycotic infection, and syphilis (9). There are various studies on the pathophysiology and management of GM in the literature; however, numerous controversies have also arisen (2,3,6,10). The present study aimed to represent and evaluate the clinicopathological findings and mark the sensitivity and resistance of isolated bacteria in patients with GM.

Patients and methods

Study setting. The present study is cross-sectional and was conducted from June 2020 to June 2022. In total, 63 female patients with a confirmed histopathological diagnosis of GM were included. Ethics approval for the present study was provided by the Ethics Committee of Sulaimani Polytechnic University (reference no. CH000120). Written informed consent was obtained from all of the individual participants included in the study.

Tissue sampling procedure. Before the intervention, a core needle biopsy was conducted for all patients for histopathological examination. The specimens were labeled and incubated in neutral buffered formalin (10%) for ~10 h at 25˚C. The tissue samples (3-μm-thick) were processed for dehydration and fixation using a tissue processor (Histo-Tek® VP1; SAKURA SEIKI Co., Ltd.) for 18-22 h. The tissues were embedded in paraffin wax to form blocks (Histo Core Arcadia H; Leica Microsystems GmbH). Hematoxylin and eosin (H&E) (Bio Optica Co, Italy) were used for staining at room temperature for 1-2 min, and the histopathological assessment was performed by a specialist histopathologist using a light microscope (Leica Microsystems GmbH).

Pathological diagnostic criteria. In the present study, the diagnostic criteria for GM were lobulocentric granulomatous inflammation in the form of well-formed epithelioid granulomas, mixed inflammation with or without giant cells and neutrophils, and the formation of abscesses.

Bacterial culture, sensitivity and resistance. In all patients, a tissue specimen was incubated in thioglycolate broth via needle aspiration, and then the samples were sent to the Microbiology Center of Smart Health Tower (Sulaymaniyah, Iraq). Four types of agar were used in the culturing process: blood agar base, chocolate agar (cat. no. 610005; Liofilchem S.r.l.), MacConkey agar (cat. no. 610028; Liofilchem S.r.l.), and Mueller-Hinton agar (cat. no. NCM0036A; Neogen). The culturing was conducted by the streak plate method with an overnight incubation at 37˚C (Heratherm IGS60; Thermo Fisher Scientific, Inc.). The bacterial identity, antibiotic sensitivity, and resistance were determined by BD Phoenix™ M50 (Becton, Dickinson and Company). A manual technique, disc diffusion by the Kirby-Bauer method, was also performed to detect antibiotic sensitivity and resistance, and Clinical and Laboratory Standards Institute (CLSI) Standards: Guidelines for Health Care Excellence (CLSI, USA; https://clsi.org/standards/products/microbiology/documents/m100/) was used for interpretation. All of the procedures were performed according to the manufacturer's instructions.

Laboratory parameters. Following an overnight fast, the blood samples were collected from the patients using tubes containing EDTA and anticoagulant-free tubes. Plasma and serum were immediately separated and stored at -80˚C prior to analysis. Five differential complete blood count (monocyte, leukocyte, neutrophil, basophil and eosinophil) evaluations were performed by fully automated Medonic M51 (Boule Medical AB). Tests for the evaluation of C-reactive protein (CRP), total IgM, IgG, and IgE, were performed by using the Cobas® 6000 analyzer series (Roche Diagnostics). The hormonal profile (thyroid stimulating hormone, prolactin and total testosterone) and interleukin-6 (IL-6) were measured using a Cobas e 411 analyzer (Roche Diagnostics). The DYNEX DSX® full-automated ELISA (Dynex Technologies Inc.) was used for the analysis of C1q, C5a, IL-17, IL-33, and the detection of *Brucella spp*. IgG and *Candida albicans*. The ChorusTrio (DIESSE Diagnostica Senese, Italy) was used to detect infections caused by the Epstein-Barr virus (EBV), cytomegalovirus (CMV), and toxoplasmosis. Integra Cobas 400 Plus (Roche Diagnostics) was used for the measurement of complements 3 and 4 (C3 and C4) and for performing anti-streptolysin O test. A rapid strip test (AccuBioTech Co., Ltd.) was conducted for the serologic diagnosis of tuberculosis.

Data collection and analysis. Patient information and medical and clinical records were acquired by using a specific questionnaire in person, or alternatively, by investigating patient medical records in the database of the Breast Center of Smart Health Tower). The records were intensively screened and evaluated. The demographic data [age at the time of admission, body mass index (BMI), family history, menopause status, menstrual cycle status, birth history, abortion history, breastfeeding, hormonal contraceptive use, drug use, clinical features of GM, laboratory findings, and immunological, microbial, and hormonal profiles were collected. The data were organized and encoded using Microsoft Excel (version 2019; Microsoft Corporation). SPSS Version 25 (IBM Corp.) was used for qualitative (only descriptive) analysis of the data.

Results

A total number of 63 female patients with GM were included in the present study. The age of the patients ranged from 24 to 50 years, with a mean age of 35.7 years. The BMI of the patients was mostly between 25 and 35. The majority of the patients were in the premenopausal or perimenopausal period. The menstrual cycle was abnormal in ~21% of the cases. Of the total number of patients, 82.5% of them had experienced >1 childbirth, and the majority had a history of breastfeeding. In a large part of the patient cohort (87.3%), breastfeeding was unilateral, with a mean duration of 41 months (Table I). The GM was unilateral in 58.7% of the patients. The most common symptom was pain (79.4%), followed by fever and chills (46%), as presented in Table II. The CMV and EBV tests were positive in all the cases. The mean ranges of the following tests were markedly elevated in comparison to the normal ranges: The erythrocyte sedimentation rate, CRP, IL-6, IL-17, C5a, white blood count, neutrophil-to-lymphocyte ratio and prolactin. The laboratory findings and immunological and hormonal profiles are summarized in (Table III). In total, nine different bacterial species were isolated from the bacterial culture of the core biopsy samples. Co-infection occurred in six cases (Table IV). The most common antibiotic resistance was recorded towards oxacillin, while 50% of the isolated bacterial species were sensitive to trimethoprim-sulfamethoxazole (Table V).

Discussion

The GM, as an inflammatory disease, is commonly described by the presence of non-necrotizing granulomas in the breast. It typically co-exhibits with numerous conditions, including breast cancer, bacterial infection, diabetes mellitus, fat necrosis, trauma, sarcoidosis and Wegener granulomatosis (11,12). The mechanism of the development of GM is considered to begin with the damage of the ductal epithelium of the breast, followed by the spreading of luminal secretions to lobular connective tissue and inducing local inflammation. Finally, lymphocytes and macrophages migrate to the region and cause a granulomatous inflammatory response (6).

Table I. Baseline characteristics of the enrolled patients with GM.

Characteristics	N (%)/mean (SD)
Age at presentation, years	35.7 (6.4) (median, 35; range, 24-50)
Menopause status	
Premenopausal/perimenopausal	60 (95.2%)
Postmenopausal	3 (4.8%)
Menarche age, years	13.4 (1.1)
Menstrual cycle status	
Normal	50 (79.4%)
Abnormal	13 (20.6%)
Birth history	
One birth	9 (14.3%)
More than one birth	52 (82.5%)
No birth	2 (3.2%)
Abortion history	
One abortion	18 (28.6%)
More than one abortion	9 (14.3%)
No abortion	36 (57.1%)
Breastfeeding	61 (96.8%)
Breastfeeding type (n=61)	
Pure	45 (73.8%)
Mixed	16 (26.2%)
Breastfeeding side (n=61)	
Unilateral	55 (87.3%)
Bilateral	6 (12.7%)
Breast feeding duration, months	41.0 (25.93)
Hormonal contraceptive use	16 (25.4%)
Anti-prolactin drug use	3 (4.8%)
Psychiatric drug use	2 (3.2%)
History of breast trauma	9 (14.3%)
BMI	28.9 (5.6)
<20	0 (0.0%)
20-25	13 (20.6%)
25-35	42 (66.7%)
>35	8 (12.7%)

GM, granulomatous mastitis; N, number of patients; SD, standard deviation; BMI, body mass index.

Table II. Clinical features of the patients with GM.

Features	N (%)
Lesion side	
Unilateral	37 (58.7%)
Bilateral	26 (41.3%)
Signs and symptoms	
Pain	50 (79.4%)
Fever/chill	29 (46.0%)
Edema	19 (30.2%)
Warmth at GM site	18 (28.6%)
Redness at GM site	17 (27.0%)
Sweating at night	2 (3.2%)
Hardness at GM site	8 (12.7%)
Core biopsy	63 (100.0%)
Number of follow-ups	4

GM, granulomatous mastitis; N, number of patients.

GM presents as a palpable mass and can be associated with different types of symptoms, including pain, erythema, sinus formation, tenderness, fever, nipple retraction, nipple discharge, and peau d'orange-like changes (2,9,11). The granulomas are usually unilateral and located in the upper outer quadrant of the breast (13). Bilateral lesions have also been reported in the literature, and they have been associated with a longer recuperation time (5). Azizi *et al* (14) conducted a study in which skin changes and nipple inversion were observed in ~20% of the patients involved. Furthermore, Kiyak *et al* (15) reported skin changes in the upper outer quadrant and areolar regions of the breast in 66% of the cases. In the study by Barreto *et al* (2), the majority of the patients presented with painful, mass-like lesions followed by erythema. In the present study, the most common symptom was pain, followed by fever and chills (46% of the cases). The lesion was unilateral in ~59% of the cases and bilateral in the remaining portion.

There is a lack of consensus on the exact etiology of GM. At present, three hypotheses have been proposed on the pathogenesis of this disease: autoimmunity response, infection disease, and hormone disorders. Some other factors, including smoking, pregnancy, breastfeeding, contraceptive drugs, and childbirth, are considered risk factors (13,16). It has been reported that women in the reproductive age or those who consume contraceptive drugs are more susceptible to being infected by GM (9). In several studies, the mean age of patients with GM was reported to be around 35 yearsold (17,18). Galactostasis, an atypical milk accumulation in the breast, can generate an autoimmune response (13). In a previous study, 59% of the cases were smokers, and almost 8% of the patients presented with BMI values >30 kg/m^2 (2). In addition, the history of passive smoking, breastfeeding duration, and the number of parturitions have also been associated with this entity (19). Some other studies have revealed the association of breastfeeding with GM, in the manner that around 83% of the cases were breastfeeding mothers (13,14,20). In this study, most of the patients were in the reproductive period, with a median age of 36 years. Most of them (81%) experienced more than one parturition. The breastfeeding history was significant in >96% of the cases. In total, 25% of the patients had consumed hormonal contraceptives, followed by anti-prolactin (4.8%) and psychiatric (3.2%) drugs. All these findings were in agreement with the previous studies; however, none of the cases were smokers, which was mentioned as a risk factor in some studies (13,16,17,19,20).

Several studies have been conducted to determine the roles of immunological patterns and hormonal imbalance in the development of GM (16,21,22). Cytokines are important proteins that regulate the response of the immune system to

Table III. Routine laboratory findings, and immunological/inflammatory and hormonal profiles in the patients with GM.

Laboratory parameters	Mean (SD)	Normal ranges	Range (min-max)
ESR	37.16 (28.62) mm/1 h	0-20 mm/1 h	1.00-128.00
CRP	17.18 (25.39) IU	<5 IU	0.32-136.00
IL-6	10.26 (10.27) IU/dl	<7 IU/dl	1.50-60.80
IL-17	78.20 (53.77) ng/ml	25-75 ng/ml	25.05-455.39
IL-33	229.93 (212.13) ng/ml	75-300 ng/ml	47.00-1439.11
IgG	12.17 (2.80) IU/dl	6-16 IU/dl	1.54-19.50
IgM	1.59 (0.55) IU/dl	0.4-2.5 IU/dl	0.81-3.08
IgE	99.57 (128.22) IU/dl	<100 IU/dl	0.96-464.60
C1q	12.91 (2.76) μg/ml	>18 μg/ml	10.93-24.28
C3	150.69 (29.25) IU/dl	91-156 IU/dl	90.00-221.10
C4	28.95 (9.55) IU/dl	20-50 IU/dl	12.40-56.20
C5a	2.95 (2.48) μg/l	0.15-0.5 μg/l	0.45-11.30
WBC	11.26 (4.01) cell/cu mm	3.5-9.50 cell/cu mm	5.94-23.81
RBC	4.59 (0.46) million/mm^3	3.8-5 million/mm^3	3.50-6.25
HGB	12.31 (1.61) g/dl	11.5-15.5 g/dl	7.06-15.20
HCT	37.20 (4.23) l/l	36-46 l/l	25.00-45.00
MCV	93.96 (101.45) f1	80-100 f1	55.90-884.00
MCH	26.920 (3.09) pg	27-32 pg	18.30-32.40
MCHC	35.98 (39.51) g/dl	31-35 g/dl	2.10-339.00
N%	70.74(10.98)	40-80	44.40-91.70
L%	23.25 (9.29)	15-45	5.80-42.50
NLR	4.02 (3.05)	1-3	1.04-15.79
M%	4.13 (2.06)	2-10	0.60-10.50
E%	1.40 (0.80)	0-4	0.10-3.70
B%	0.47 (0.22)	0-1	0.04-1.00
P	333.11 (84.83) $10^3/\mu$	150-400 $10^3/\mu$	127.00-535.00
PCT%	0.29 (0.06)	0.19-0.39	0.16-0.44
AST	18.92 (15.57) IU/Meq	<32 IU/Meq	5.00-129.00
ALT	20.58 (13.14) IU/Meq	<35 IU/Meq	4.90-87.40
Blood sugar	119.36 (33.54) Mg/100ml	70-120 Mg/100 ml	76.00-232.70
Cholesterol	175.80 (35.39) Mg/100 ml	150-200 Mg/100 ml	100.00-270.00
Calcium	9.43 (0.42) Mg/100ml	8.6-10 Mg/100 ml	8.10-10.20
TSH	2.23 (4.05) IU/ml	0.27-4.2 IU/ml	0.13-31.47
Prolactin	32.56 (46.63) ng/ml	3.8-23 ng/ml	1.91-299.90
Testosterone	0.49 (3.14) ng/ml	0.08-0.48 ng/ml	0.02-25.00

GM, granulomatous mastitis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood count; RBC, red blood count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; TSH, thyroid stimulating hormone; N%, neutrophil; L%, leukocyte; M%, monocyte; E%, eosinophil; B%, basophil; P, platelets.

foreign bodies and antigens. Furthermore, they can prompt local and systemic inflammatory responses. Several interleukins (IL-17, IL-22, and IL-23) can be involved in triggering autoimmune diseases by taking advantage of two factors: Their significant role in inflammatory processes and their capability to induce the accumulation of proinflammatory cells (16). In a study on IL-33 as an inflammatory marker in the differential diagnosis of breast cancer and GM, it was claimed that patients with GM have higher levels of IL-33 (21). Another study by Huang *et al* (5) revealed that serum CRP and IL-6 can be depended on as biomarkers for the severity of GM. Hormonal imbalances, including the elevation of estrogen, progesterone, and prolactin have been mentioned to be associated with the pathogenesis of GM (2). Another study demonstrated that elevated prolactin prolongs the duration of the disease and also increases the rate of recurrence (22). A hypothesis was proposed, stating that prolactin activates the nuclear factor-κB pathway of mammary epithelial cells and inflammatory factors like IL-1, IL-6, interferon-c, tumor necrosis factor-a. Inflammatory factors can induce an inflammatory response of

Table IV. Microbial profile in the patients with GM.

Microbes	No. patients (%)/ no. of isolates
Viruses	
CMV	63 (100%)
EBV	63 (100%)
HBsAg	0 (0%)
Toxoplasma gondii	16 (25.4%)
Candida spp.	2 (3.2%)
Bacterial culture (total number of isolates, 16)	14 (22.2%)
Burkholderia cepacia	5 (31.25%)
Staphylococcus epidermidis	3 (18.75%)
Staphylococcus hominis	2 (12.5%)
Unknown gram-positive bacteria	1 (6.25%)
Staphylococcus aureus	1 (6.25%)
Acinetobacter baumannii	1 (6.25%)
Staphylococcus pettenkoferi	1 (6.25%)
Staphylococcus kloosii	1 (6.25%)
Corynebacterium jeikeium	1 (6.25%)
Mycobacterium tuberculosis (serologic)	0 (0.0%)
Brucella spp. (serologic)	6 (9.5%)
Co-infections	6 (9.5%)
Burkholderia cepacia and *Toxoplasma gondii* co-infection	1
Staphylococcus epidermidis and *Toxoplasma gondii* co-infection	1
Burkholderia cepacia and *Toxoplasma gondii* co-infection	1
Burkholderia cepacian, *Staphylococcus kloosii* and *Toxoplasma gondii* co-infection	1
Staphylococcus epidermis and *Brucella spp*. co-infection	1
Candida spp. and *Brucella spp*. co-infection	1

GM, granulomatous mastitis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBsAg, hepatitis B virus antigen.

the interlobular stroma and result in abscess formation (23,24). In the present study, CRP levels were increased, with a mean level of 17.18 IU. The present study supports the findings of the previously mentioned studies (23,24) with regard to the effects of immunological patterns and prolactin hormone, since IL-6, IL-17, and prolactin were significantly increased.

Even though the role of pathogenic bacteria in the occurrence of GM is not yet well established, it has been reported that Gram-positive bacteria may be involved in the progression of GM. Several types of bacterial flora, including *Corynebacterium, Streptococci* and *Propionibacterium,* have been isolated from the discharge of GM (13). In the study by Taylor *et al* (25), *Corynebacterium* was isolated in the breast tissue of ~55% of patients. Another study reported that *Corynebacterium kroppenstedtii* was the most commonly isolated species in patients with GM (26). In the present study, bacterial culture was conducted for the tissue biopsies of 14 patients, and *Burkholderia cepacia* was the most common isolated bacterium, followed by *Staphylococcus epidermidis*. A previous study revealed that bacterial infections, particularly those caused by *Mycobacterium tuberculosis*, can cause granulomas and chronic inflammatory responses. These factors can be involved in the occurrence of GM or deteriorate the disease into being increasingly aggressive. Therefore, prolonged antibiotic courses have been recommended to prevent the further progression of the disease and provide more effective treatment (27).

One of the major perspectives in the present study was the testing of 46 types of antibiotics to determine which of the isolated bacteria has the highest level of sensitivity and resistance and is better to control the growth of the isolates. This can aid clinicians in the selection of antibiotics to restrict the growth of those bacteria that may prolong the period and severity of the disease. The use of oxacillin exhibited the lowest sensitivity, while antibiotic sensitivity was at its highest for trimethoprim-sulfamethoxazole.

Core needle biopsy plays a crucial role in the definitive diagnosis of GM and in ruling out other diagnoses, including ductal ectasia, fungal infection and sarcoidosis (2,12). All the patients involved in the present study were diagnosed with GM, according to the corresponding histopathological evaluation.

The small sample size, the short duration of the study, and the lack of a proper statistical comparison due to the aggressiveness of the condition are the main limitations of the present study.

Table V. Sensitivity and resistance to antibiotics among the isolated bacterial species.

	Resistance		Sensitivity	
Antibiotics	No. of isolates (n=16)	Bacterial species (n)	No. of isolates (n=16)	Bacterial species (n)
Amikacin	3 (18.75%)	BC (3)	6 (37.5%)	AB, BC, CJ, SA, SE, UK
Amocillin-clavulanate	7 (43.75%)	AB, BC (4), SE, SH	-	-
Amoxicillin	4 (25.0%)	BC (3), SE	-	-
Amoxiclav	-	-	1 (6.2%)	SA
Ampicillin	7 (43.75%)	AB, BC, CJ, SE, SH, SK, SP	-	-
Azithromycin	1 (6.25%)	CJ	1 (6.2%)	SA
Aztreonam	1 (6.25%)	SA	-	-
Cefazolin	4 (25.0%)	AB, BC (3)	-	-
Cefepime	1 (6.25%)	BC	2 (12.5%)	AB, SE
Cefotaxime	4 (25.0%)	BC, SH (2), SK	3 (18.7%)	AB, BC, SA
Cefoxitin	1 (6.25%)	CJ	-	-
Ceftazidime	4 (25.0%)	CJ, SA, SE, UB	5 (31.2%)	AB, BC (2), SE (2)
Ceftriaxone	4 (25.0%)	BC (3), SA	2 (12.5%)	AB, SE
Cefuroxime	4 (25.0%)	AB, BC (2), SE	-	-
Cephalexin	-	-	3 (18.7%)	BC, SA, SE, UK
Ciprofloxacin	2 (18.75%)	SE, SH	6 (37.5%)	AB, BC (2), SA, SE, SK
Clindamycin	4 (25.0%)	BC (2), CJ, SK	6 (37.5%)	AB, SA, SE, SH, SP, UK
Chloramphenicol	-	-	1 (6.2%)	SE
Cloxacillin	1 (6.25%)	BC	-	-
Daptomycin	-	-	3 (18.7%)	BC, SE, SH
Doxycycline	-	-	1 (6.2%)	SA
Ertapenem	3 (18.75%)	AB, BC (2)	-	-
Erythromycin	6 (37.5%)	BC (2), SE, SH (2), SK	-	-
Ceftolozane/tazobactam	-	-	1 (6.2%)	BC
Gentamycin	7 (43.75%)	BC (4), SE, SK, UB	7 (43.7%)	AB, BC, SA, SE (2), SH, SP
Imipenem	2 (18.75%)	BC (2)	2 (12.5%)	AB, BC
Lincomycin	-	-	1 (6.2%)	BC
Levofloxacin	2 (18.75%)	CJ, SH	3 (18.7%)	BC (2), SE
Lincomycin	2 (18.75%)	AB, BC	-	-
Linezolid	-	-	1 (6.2%)	SP
Meropenem	-	-	4 (25%)	BC (2), SE, UK
Moxifloxacin	-	-	2 (12.5%)	SA, SK
Mupirocin	1 (6.25%)	SP	3 (18.7%)	BC, SE, SK
Nalidixic acid	-	-	-	-
Nitrofurantoin	7 (43.75%)	AB, BC (3), SE, SK, SP	3 (18.7%)	BC, SE, SH
Norfloxacin	1 (6.25%)	CJ	1 (6.2%)	SE
Oxacillin	8 (50.0%)	BC, SA, SE, SH (2), SK, SP, UB	1 (6.2%)	SE
Penicillin G	5 (31.25%)	SE (2), SH (2), SP	-	-
Piperacillin-Tazobactam	2 (18.75%)	BC (2)	3 (18.7%)	AB, SE (2)
Rifampicin	2 (18.75%)	BC, UB	6 (37.5%)	BC, CJ, SA, SE, SH, SP
Teicoplanin	1 (6.25%)	SK	4 (25%)	BC, SE, SH, SP
Tetracycline	1 (6.25%)	CJ	5 (31.2%)	AB, BC, SA, SE, SP
Tigecycline	2 (18.75%)	BC, SE	-	-
Tobramycin	-	-	2 (12.5%)	AB, SE
Trimethoprim-sulfamethoxazole	4 (25.0%)	CJ, SA, SH, SK	8 (50%)	BC (4), SE (2), SH, SP
Vancomycin	2 (18.75%)	BC, SK	6 (37.5%)	AB, BC, CJ, SA, SE, UK

AB, *Acinetobacter baumannii*; BC, *Burkholderia cepacian*; CJ, *Corynebacterium jeikeium*; SA, *Staphylococcus aureus;* SE, *Staphylococcus epidermidis*; SH, *Staphylococcus hominis*; SK, *Staphylococcus kloosii*; SP, *Staphylococcus pettenkoferi*; UB, unknown Gram-positive bacteria.

In conclusion, there is no consensus on the etiology of GM. Any studies related to this aspect expand our current understanding of this mysterious condition. Conducting bacterial cultures and sensitivity tests aids in the determination of the best antibiotic to decrease the duration and morbidity of this disease.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

NKE performed the data collection and the patient follow-up. AMS and ZDH supervised the present study and majorly contributed to the conception of the study, as well as in the literature search for related studies. LRAP performed the radiological assessment of granulomatous mastitis. AMA performed the histopathological analysis for the cases. GSA, BAA and RQS performed the literature review, and analyzed and interpreted the data. FHK and HOA were involved in reviewing the literature, in the writing of the manuscript, and in data analysis and interpretation. NKE and AMS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval for the present study was provided by the Ethics Committee of Sulaimani Polytechnic University (reference no. CH000120). Written informed consent was obtained from all of the individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kessler E and Wolloch Y: Granulomatous mastitis: A lesion clinically simulating carcinoma. Am J Clin Pathol 58: 642-646, 1972.
2. Barreto DS, Sedgwick EL, Nagi CS and Benveniste AP: Granulomatous mastitis: Etiology, imaging, pathology, treatment, and clinical findings. Breast Cancer Res Treat 171: 527-534, 2018.
3. Bayrak BY, Cam I, Eruyar AT and Utkan NZ: Clinicopathological evaluation of idiopathic granulomatous mastitis patients: A retrospective analysis from a tertiary care hospital in Turkey. Ann Diagn Pathol 55: 151812, 2021.
4. Benson JR and Dumitru D: Idiopathic granulomatous mastitis: Presentation, investigation and management. Future Oncol 12: 1381-1394, 2016.
5. Huang YM, Lo C, Cheng CF, Lu CH, Hsieh SC and Li KJ: Serum C-reactive protein and interleukin-6 levels as biomarkers for disease severity and clinical outcomes in patients with idiopathic granulomatous mastitis. J Clin Med 10: 2077, 2021.
6. Altintoprak F, Karakece E, Kivilcim T, Dikicier E, Cakmak G, Celebi F and Ciftci IH: Idiopathic granulomatous mastitis: An autoimmune disease? ScientificWorldJournal 2013: 148727, 2013.
7. Alsaleh N: Assertive clinical practice in managing patients with idiopathic granulomatous mastitis: Review of literature. Ann Med Surg (Lond) 70: 102792, 2021.
8. Altieri M, Barra F, Casabona F, Soriero D, Gustavino C and Ferrero S: Idiopathic granulomatous mastitis: Etiopathogenetic considerations on a rare benign inflammatory breast disease. J Invest Surg 34: 998-999, 2021.
9. Aghajanzadeh M, Hassanzadeh R, Alizadeh Sefat S, Alavi A, Hemmati H, Esmaeili Delshad MS, Emir Alavi C, Rimaz S, Geranmayeh S, Najafi Ashtiani M, *et al*: Granulomatous mastitis: Presentations, diagnosis, treatment and outcome in 206 patients from the north of Iran. Breast 24: 456-460, 2015.
10. Esmaeil NK, Salih AM, Pshtiwan LRA, Muhialdeen AS, Abdullah AM, Hama JI, Hammood ZD, Kakamad FH, Tahir SH, Abdalla BA, *et al*: Management of idiopathic granulomatous mastitis: A single institution experience. Breast Care: 1-8, 2023.
11. Larsen LH, Peyvandi B, Klipfel N, Grant E and Iyengar G: Granulomatous lobular mastitis: Imaging, diagnosis, and treatment. AJR Am J Roentgenol 193: 574-581, 2009.
12. Choi SH, Jang KS and Chung MS: Bilateral granulomatous mastitis with a different etiology. Cancer Biomarkers 15: 333-338, 2015.
13. Yin Y, Liu X, Meng Q, Han X, Zhang H and Lv Y: Idiopathic granulomatous mastitis: Etiology, clinical manifestation, diagnosis and treatment. J Invest Surg 35: 709-720, 2022.
14. Azizi A, Prasath V, Canner J, Gharib M, Sadat Fattahi A, Naser Forghani M, Sajjadi S, Farhadi E, Vasigh M, Kaviani A, *et al*: Idiopathic granulomatous mastitis: Management and predictors of recurrence in 474 patients. Breast J 26: 1358-1362, 2020.
15. Kiyak G, Dumlu EG, Kilinc I, Tokaç M, Akbaba S, Gurer A, Ozkardes AB and Kilic M: Management of idiopathic granulomatous mastitis: Dilemmas in diagnosis and treatment. BMC Surg 14: 66, 2014.
16. Saydam M, Yilmaz KB, Sahin M, Yanik H, Akinci M, Yilmaz I, Balas S, Azili C and Gulcelik MA: New findings on autoimmune etiology of idiopathic granulomatous mastitis: Serum IL-17, IL-22 and IL-23 levels of patients. J Invest Surg 34: 993-997, 2021.
17. Al-Khaffaf B, Knox F and Bundred NJ: Idiopathic granulomatous mastitis: A 25-year experience. J Am Coll Surg 206: 269-273, 2008.
18. Velidedeoglu M, Kilic F, Mete B, Yemisen M, Celik V, Gazioglu E, Ferahman M, Ozaras R, Yilmaz MH and Aydogan F: Bilateral idiopathic granulomatous mastitis. Asian J Surg 39: 12-20, 2016.
19. Pak H, Maghsoudi LH, Soltanian A and Jafarinia S: Evaluation of clinical manifestation and risk factors of idiopathic granulomatous mastitis. Int J of Surg Open 35: 100380, 2021.
20. Gurleyik G, Aktekin A, Aker F, Karagulle H and Saglamc A: Medical and surgical treatment of idiopathic granulomatous lobular mastitis: A benign inflammatory disease mimicking invasive carcinoma. J Breast Cancer 15: 119-123, 2012.
21. Yigitbasi MR, Guntas G, Atak T, Sonmez C, Yalman H and Uzun H: The role of interleukin-33 as an inflammatory marker in differential diagnosis of idiopathic granulomatous mastitis and breast cancer. J Invest Surg 30: 272-276, 2017.
22. Erhan Y, Veral A, Kara E, Ozdemir N, Kapkac M, Ozdedeli E, Yilmaz R, Koyuncu A, Erhan Y and Ozbal O: A clinicopthologic study of a rare clinical entity mimicking breast carcinoma: Idiopathic granulomatous mastitis. Breast 9: 52-56, 2000.
23. Boutet P, Sulon J, Closset R, Detilleux J, Beckers JF, Bureau F and Lekeux P: Prolactin-induced activation of nuclear factor kappaB in bovine mammary epithelial cells: Role in chronic mastitis. J Dairy Sci 90: 155-164, 2007.
24. Cserni G and Szajki K: Granulomatous lobular mastitis following drug-induced galactorrhea and blunt trauma. Breast J 5: 398-403, 1999.

25. Taylor GB, Paviour SD, Musaad S, Jones WO and Holland DJ: A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. Pathology 35: 109-119, 2003.
26. Kıvılcım T, Altıntoprak F, Memiş B, Ferhatoğlu MF, Kartal A, Dikicier E, Ciftçi İH and Dilek FH: Role of bacteriological agents in idiopathic granulomatous mastitis: Real or not? Eur J Breast Health 15: 32-36, 2018.
27. Williams MS, McClintock AH, Bourassa L and Laya MB: Treatment of granulomatous mastitis: Is there a role for antibiotics? Eur J Breast Health 17: 239-246, 2021.