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Bilateral Idiopathic Granulomatous Mastitis: Outcomes of a Tertiary Hospital

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ABSTRACT

Introduction: Bilateral granulomatous mastitis (BIGM) is a rare bilateral inflammatory pseudotumor of the breast. This study presented the clinical characteristics of BIGM and our treatment results.

Methods: Thirteen patients who met the diagnostic criteria for BIGM were included in the study. The anamnesis and the results of the physical examination, clinical radiology, histopathology, microbiology, and treatment were recorded and analyzed.

Results: The mean age of the patients was 36.23±8.98 years (range: 25 to 53 years). In the first session of the treatment, recurrence was observed in all (100%) patients. Until remission, the distribution of treatment methods in patients with BIGM (n=13) was as follows: 61.5% bilateral combined medical (BCM) treatment, 15.4% bilateral combined medical treatment plus surgery (BCMS), 23.1% unilateral combined medical treatment/unilateral combined medical treatment plus surgery (UCM/UCMS). The distribution of treatment methods in patients (n=26) in the unilateral subgroup was as follows: 73.1% UCM treatment and 26.9% UCMS. There was no significant difference (p>0.05) between the distributions of the patients' combined treatments. However, durations of remission (p=0.018) and follow-up (p=0.037) were significantly longer in young (p=0.037) patients.

Conclusion: Although there is no significant (p>0.05) difference between patients' combined (BCM, BCMS, UCM/UCMS, UCM, UCMS) treatment methods, the first choice for treating patients with BIGM is medical treatment methods. Surgery can be performed for patients who are resistant to medical treatment.

Keywords: Granulomatous mastiti, idiopathic, breast cancer, tuberculosis, disease treatment

Introduction

Non-specific or idiopathic granulomatous mastitis (IGM), which was first introduced by Kessler and Wolloch (1), is a benign chronic inflammatory disease of the breast, characterized by non-caseating granulomas. There is no epidemiological evidence in the literature; however, there are large case series reported from all over the worldwide, mostly from Eurasian countries (1,2). In the differential diagnosis, breast cancers are confused with pyogenic and granulomatous infectious or non-infectious inflammatory diseases of the breast (1,3-6). The underlying etiology is not yet known (2). Definitive diagnosis is made by histopathological evaluation and exclusion of a descriptive etiology (2-6).

IGM without a definitive etiology is theoretically considered sterile. However, empirical antibiotics and/or abscess drainage (percutaneous/incisional) are applied to patients with mastitis and/or the signs of abscess on physical examination. There are options such as conservative treatment, glucocorticoids, methotrexate, colchicine, imuran (azathioprine), non-steroidal anti-inflammatory drugs (NSAID), and surgery (local excision, mastectomy) for treating patients diagnosed with IGM histopathologically (3,4,6-10). Although there are different opinions on the management of the disease, treatment with glucocorticoids (local or systemic) and/or their combination (glucocorticoids plus methotrexate) is still the dominant treatment modality due to the autoimmune and inflammatory origin of IGM (8,9). However, despite different treatment methods available, recurrence rates range, 5% to 50% have been reported in unilateral idiopathic granulomatous mastitis (UIGM). This rate is much higher in patients with bilateral idiopathic granulomatous mastitis (BIGM) (10,11).

As far as we know, the incidence of BIGM is quite rare, except for a few case reports in the literature. This study presents the outcomes of the patients who were treated and followed up with the diagnosis of BIGM between 2010 and 2022.

Methods

This study was conducted in line with the ethical standards defined by the Institutional Research Committee and the Helsinki Declaration dated 1964. Before the study, ethics committee approval was obtained

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from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 06, date: 13.01.2023).

Patient selection: The medical data of the patients who were approved with the preliminary diagnosis of BIGM were scanned retrospectively from the archives. Patients (n=13) with a confirmed diagnosis of BIGM were included in the study. Patients with a diagnosis of breast cancer, unilateral IGM, and specific GM were excluded from the study (Figure 1).

Diagnosis, treatment, and follow-up: Medical archives were retrospectively scanned for patients with the preliminary diagnosis of BIGM and patient data including complaints, anamnesis, and the results of the physical examination, hemogram, basic biochemistry test, serology tests, tissue biopsy (tru-cut and/or excisional and/or abscess wall), and cultures; radiological data including breast ultrasonography (USG) and/or magnetic resonance imagining (MRI) to evaluate involvement, and mammography (MMG) results for the patients aged over 40 years.

To confirm the BIGM diagnosis, we checked tissue biopsies (tru-cut and/or excisional and/or abscess wall) collected separately from each breast, lymphocytes with non-caseating granulomas, plasma cells, epithelioid histiocytes rarely accompanied by eosinophils in or around lobules, Langhans giant cells, microorganisms [Gram staining for bacteria, Periodic acid-Schiff (PAS) staining for fungi, Erlich-Ziehl-Neelsen (EZN)/polymerase chain reaction (PCR) for mycobacterium tuberculosis (TBC)] and purified protein derivative (PPD) negativity (<10 mm). Moreover, the negativity of a descriptive etiology (parasitic, fungal, bacterial) was confirmed with the culture inoculation and microscopic examinations of the biopsy samples. The results of the preoperative hemogram, basic biochemistry tests, chest X-ray to exclude sarcoidosis, and serology tests to exclude brucellosis and hepatitis were checked. The final status of the patients who had missing data in the medical archives and/or who could not come for a follow-up visit due to address change was updated by making phone calls.

Until the clinicopathological results of the patients with mastitis symptoms in the breast were obtained, these patients received empirical antibiotherapy, NSAID treatment, and drainage in the presence of an abscess (percutaneous or incisional) for 10 to 20 days. The empirical antibiotherapies of the patients were arranged by a specialist physician at the polyclinic, considering the side effects. Treatment options approved by patients with the clinicopathological diagnosis of IGM were oral systemic glucocorticoids, methotrexate, conservative treatment [antibiotherapy and drainage (incisional/percutaneous) in the presence of abscess], and surgery, respectively. Oral systemic glucocorticoids (0.5 to 1 mg/kg/day) were started in moderate/high doses (7.5 to 100 mg/day) and gradually decreased after treatment, which lasted for a minimum of 3 weeks and a maximum of 8 weeks. One patient was treated with methotrexate at a dose of 15 mg/week administered in 2 divided doses for 6 months. Due to the toxic side effects of methotrexate (hematotoxic/hepatotoxic), hemogram and biochemistry tests were performed every two months to check patients' well-being. During treatment, patients were started on calcium, vitamin D, proton pump inhibitor, and folic acid to eliminate the influence of the side effects of glucocorticoids sand methotrexate. Conservative treatment was followed by empirical antibiotherapy and drainage (percutaneous or incisional) in case of mastitis and/or breast abscess. Conservative treatment was followed by empirical antibiotherapy and drainage (percutaneous or incisional) in case of mastitis and/or breast abscess.

After the treatment, clinical regression of inflammation in the breast, closure of fistulas, regression of existing skin lesions, and/or USG findings, and no recurrence of the disease during the follow-up period were accepted as remission. Resistance to therapy during treatment and/or relapse of the disease after the treatment was considered a recurrence. The subjects whose disease recurred were informed about the treatment options and the treatment they approved was started to be administered till remission was achieved. For patients who achieved remission and who attended regular follow-up visits, follow-up visits were scheduled once every three months for 1 year and then once a year. Follow-up visits include a physical examination and USG examination of the patients. The patients who did not attend their follow-up visits due to a change in their address or restrictions due to the COVID-19 pandemic were called to obtain information about their treatment, follow-up, and final health status.

Study design: Demographic data, physical examination results, and data regarding any diagnosed diseases or concomitant chronic disorders were recorded from the medical archives of the patients. The radiologically measured size/dimensions of the masses were recorded. The treatment options approved by the patients before and after histopathological diagnosis (empirical antibiotherapy plus NSAID) were conservative therapy, glucocorticoids, glucocorticoids plus methotrexate therapy, and resection or mastectomy with intact margins. Treatment, follow-up, and remission durations of the patients were calculated based on the day the first treatment was started. All combined (1st session, 2nd session, 3 sessions, 4th session, etc.) therapies administered to patients before and after clinicopathological diagnosis (empirical antibiotherapy plus NSAID) were analyzed under the groups of bilateral combined medical (BCM), bilateral combined medical plus surgery (BCMS), unilateral combined medical/unilateral combined medical plus surgery (UCM/UCMS), UCM, and UCMS.

Statistical Analysis

We used the descriptive statistics of mean, standard deviation, median, minimum, maximum, frequency, and ratio. Quantitative parametric independent data were analyzed using the Independent samples t-test and ANOVA. Quantitative non-parametric independent data were analyzed using the Kruskal-Wallis and the Mann-Whitney U tests. Quantitative independent data were analyzed using the chi-square test, but when the conditions for the chi-square test were not met, we used the Fisher's exact test. The SPSS 26.0 program was used for the analysis.

Results

The prevalence of BIGM was 3.03% (13/428) in all granulomatous mastitis cases and 3.59% (13/362) in IGM, and the mean age of the patients was 36.23±8.98 (range: 25.0 to 53.0) years. In the bilateral and unilateral evaluations, the mean age of patients who had IGM in the right breast was 36.69±8.97 years (range: 25 to 53 years), of those who had IGM in the left breast was 36.77±9.24-year (range: 25 to 53

years) and 36.77±8.89 years (range: 25 to 53 years). All patients (100%) had a history of giving birth and breastfeeding at least once, and 84.6% of them were premenopausal. Of all patients, 15.4% had a history of tobacco use, 7.7% of trauma, 15.4% of oral contraceptive (OC) use, and 38.5% of them had a history of systemic disease. As a history of systemic disease, two patients had type 2 diabetes mellitus (DM), one patient had hypertension (HT), one patient had DM plus HT, and one patient had Hashimoto thyroiditis (HsT). The patients had no history of exposure to galactorrhea, galactocele, hyperprolactinemia, rheumatology, or tuberculous. The most common symptoms and signs (100%) were breast mass and inflammation. At the time of diagnosis, the mean size of the masses in the right breast was 4.98±2.65 cm and the mean size of the masses in the left breast was 3.38±1.25 cm. The presentation of the disease was bilateral in 46.2% of the patients, in the right breast in 23.1%, in the left breast in 30.8%, and the disorder was synchronous in 53.8% and metachronous in 46.2% (Figure 1, Table 1).

The distribution of the patients according to the radiological examinations applied was as follows: 23.1% bilateral USG, 30.8% bilateral USG and MRI, 15.5% bilateral USG plus MRI plus MMG, and the radiological distribution was different between the sides in 30.8% of the patients. The method used in the histopathological diagnosis of the patients was 30.8% bilateral abscess wall, 53.8% bilateral tru-cut

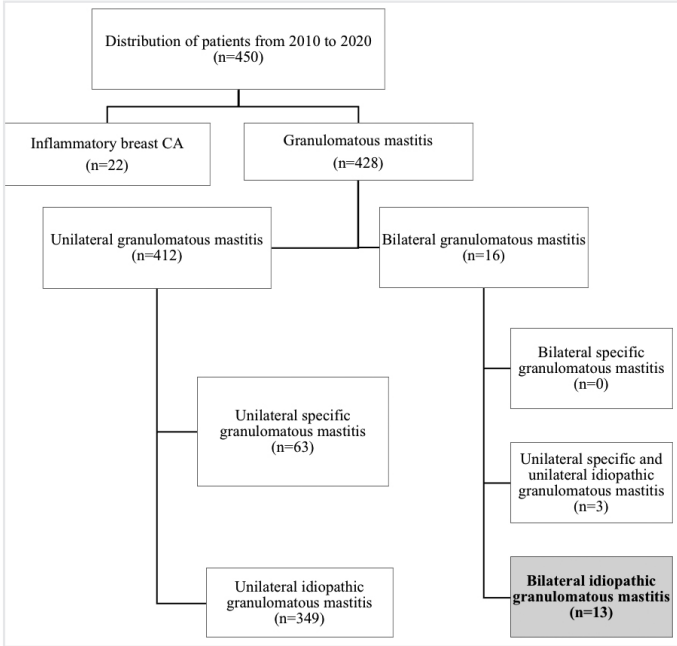

Figure 1. Distribution of patients

Table 1. Demographic and clinicopathological distributions of patients with bilateral idiopathic granulomatous mastitis

			Min.-max.	Median	Mean ± SD-% (n)
Age (year)	B		25.00-53.00	34.00	36.23±8.98
	R		25.00-53.00	35.00	36.69±8.97
	L		25.00-53.00	34.00	36.77±9.24
	U		25.00-53.00	35.00	36.77±8.89
Menopausal status	B/R/L/U	Premenopause			84.6% (11)/84.6% (11)/84.6% (11)/84.6% (22)
	B/R/L/U	Menopause			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
Pregnancy	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Breastfeeding	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Smoking	B/R/L/U	+			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
	B/R/L/U	-			84.6% (11)/84.6% (11)/84.6% (11)/84.6% (22)
Trauma	B/R/L/U	+			7.7% (1)/7.7% (1)/7.7% (1)/7.7% (2)
	B/R/L/U	-			92.3% (12)/92.3% (12)/92.3% (12)/92.3% (24)
OC	B/R/L/U	+			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
	B/R/L/U	-			84.6% (11)/84.6% (11)/84.6% (11)/84.5% (22)
TBC exposure	B/R/L/U	-			100% (13)/100% (13)/100% (13)/100% (26)
Systemic disease	B	+			38.5% (5)
	B	-			61.5% (8)
Size of mass (cm)	R		2.20-12.00	4.50	4.98±2.65
	L		1.90-6.00	3.00	3.38±1.25
	U		1.90-12.00	3.00	4.18±2.19
Mass	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Inflammation	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Fistula	B/R/L/U	+			23.1% (3)/38.5% (5)/53.8% (7)/46.2% (12)
	B/R/L/U	-			38.5% (5)/61.5% (8)/46.2% (6)/53.8% (14)
	B	(+/-)			38.5% (5)
Nipple retraction	B/R/L	+			7.7% (1)/15.4% (2)/23.1% (3)/19.2% (5)

biopsy, 30.8% unilateral abscess wall, or tru-cut biopsy. There was no reproduction in the cultures (aerobic, anaerobic, and fungal cultures). The methods used to confirm the TBC negativity of the patients were as follows: 30.8% bilateral TBC PCR, 46.2% bilateral EZN, 7.7% bilateral PPD, and 15.4% unilateral TBC PCR or EZN (Table 1).

Because to the synchronous/metachronous onset of the disease, there are differences between patients in terms of mean age, total treatment time, total remission time, and total follow-up time. In patients with BIGM, the mean total treatment duration was 32.04±22.00 months (range: 3.37 to 69.90 months), the mean total remission duration was

Table 1. continued

			Min.-max.	Median	Mean ± SD-% (n)
	B/R/L/U	-			69.2% (9)/84.6% (11)/76.9% (10)/80.8% (21)
	B	+/-			23.1 (3)
Erythema nodosum	B/R/L/U	+			7.7% (1)/7.7% (1)/7.7% (1)/7.7% (2)
	B/R/L/U	-			92.3% (12)/92.3% (12)/92.3% (12)/92.3% (24)
Abscess drainage	B/R/L/U	+			53.8% (7)/84.6% (11)/61.5% (8)/73.1% (19)
	B/R/L	-			7.7% (1)/15.4% (2)/38.5% (5)/26.9% (7)
	B	(+/-)			38.5% (5)
Diagnosis of tissues	B/R/L	Abscess wall			30.8% (4)/30.8% (4)/38.5% (5)
	B/R/L	Tru-cut			53.8% (7)/69.2% (9)/61.5% (8)
	B	Abscess wall/ tru-cut			15.4% (2)
TBC test	B/R/L	TBC PCR (-)			30.8% (4)/38.5% (5)/38.5% (5)
	B/R/L	EZN (-)			46.2% (6)/53.8% (7)/53.8% (7)
	B/R/L	Anergic PPD			7.7% (1)/7.7% (1)/7.7% (1)
	B	TBC PCR (-)/EZN (-)			15.4% (2)
Culture	B/R/L/U	(-)			100% (13)/100% (13)/100% (13)/100% (26)
Radiology	B/R/L/U	USG			23.1% (3)/30.8% (4)/38.5% (5)/34.6% (9)
	B/R/L/U	USG + MMG			0.0% (0)/7.7% (0)/0.0% (0)/3.8% (1)
	B/R/L/U	USG + MRI			30.8% (4)/53.8% (7)/46.2% (6)/50.0% (13)
	B/R/L/U	USG + MMG + MRI			15.4% (2)/7.7% (1)/15.4% (2)/11.5% (3)
	B	Other			30.8% (4)
The first side affected	B/R/L				46.2% (6)/23.1% (3)/30.8% (4)
Synchronous/metachronous					53.8%/46.2%
Differences between the sides in terms of duration			0.00-67.73	5.00	10.86±19.36
Total treatment duration (months)	B		3.37-69.90	29.50	32.04±22.00
	R		0.73-66.37	10.06	15.52±17.98
	L		1.00-69.90	29.50	25.87±24.21
	U		0.73-69.90	10.62	20.70±21.55
Total remission duration (months)	B		3.30-88.93	37.87	40.40±27.61
	R		3.30-170.90	50.57	58.84±47.05
	L		6.00-88.93	51.40	46.80±26.96
	U		3.30-170.90	50.98	52.82±38.07
Total follow-up duration (months)	B		9.37-115.97	76.80	76.44±34.83
	R		9.37-177.80	69.40	74.36±45.10
	L		9.37-109.07	80.90	72.67±33.73
	U		9.37-177.80	79.02	73.52±39.59

Min.-max.: Minimum-maximum, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, TBC: Mycobacterium tuberculosis, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-), TBC PCR: Mycobacterium tuberculosis polymerase chain reaction, Tru-cut: Core needle biopsy, EZN: Erlich-Ziehl-Neelsen, PPD: Purified protein derivative, USG: Ultrasonography, MMG: Mammography, MRI: Magnetic resonance imaging

40.40±27.61 months (range: 3.30 to 88.93 months), and the mean total follow-up duration was 76.44±34.83 months (range: 9.37 to 177.77 months). In the unilateral evaluation, the mean total treatment duration was 20.70±21.55 months (range: 0.73 to 69.90 months), the mean total remission duration was 52.82±38.07 months (range: 3.30 to 170.90), and the mean total follow-up duration was 73.52±39.59 months (range: 9.37 to 177.80 months). For patients with IGM in the right breast, the mean total treatment duration was 15.52±17.98 months (range: 0.73 to 69.90 months), the mean total remission duration was 58.84±47.05 months (range: 3.30 to 88.93 months), and the mean total follow-up duration was 74.36±45.10 months (range: 9.37 to 177.77 months). In patients with IGM in the left breast, the mean total treatment duration was 25.87±24.21 months (range: 1.0 to 69.90 months), the mean total remission duration was 46.80±26.96 months (range: 6.0 to 88.93 months), and the mean total follow-up duration was 72.67±33.73 months (range: 9.37 to 177.77 months). In the bilateral evaluation of combined treatments administered to patients before and after clinicopathological diagnosis, recurrence rates in at least one breast were 100%, 92.3%, 30.3%, and 0%, respectively. The unilateral recurrence rate were 96.2%, 69.2%, and 19.2%, respectively. All patients achieved remission after receiving combined therapies. The incidence rate of side effects in patients receiving combined therapy was 69.2% (n=9), and all of them received glucocorticoid therapy (Table 1, 2).

After combined therapies, all patients achieved remission. The distribution of patients receiving bilateral combined therapies was as follows: 61.5% (8/13) BCM, 15.4% (2/13) BCMS, and 23.1% (3/13) BCM/BCMS. The distribution of patients receiving unilateral combined therapies was as follows: 73.1% (19/26) UCM and 26.9% (7/26) UCMS. No

Table 2. Treatment distribution, recurrence and remission

			Right	Left	Unilateral	Bilateral
			% (n)	% (n)	% (n)	% (n)
Before clinicopathological diagnosis	Treatment 1	Antibiotherapy + NSAID	100% (13)	100% (13)	-	-
	Remission		7.7% (1)	0 (0)	3.8 (1)	0 (0)
	Recurrence		92.3% (12)	100% (13)	96.2% (25)	100% (13)
After clinicopathological diagnosis	Treatment 2	Glucocorticoids	30.8% (4)	23.1% (3)	-	-
		Glucocorticoids + methotrexate	7.7% (1)	7.7% (1)	-	-
		Conservative treatment	53.8% (7)	69.2% (9)	-	-
		Surgery	7.7% (1)	0% (0)	-	-
	Remission		30.8% (4)	30.8% (4)	30.8% (8)	7.7% (1)
	Recurrence		69.2% (9)	69.2% (9)	69.2% (18)	92.3% (12)
	Treatment 3	Glucocorticoids	23.1% (3)	46.2% (6)	-	-
		Glucocorticoids + methotrexate	0% (0)	0% (0)	-	-
		Conservative treatment	30.8% (4)	15.4% (2)	-	-
		Surgery	15.4% (2)	7.7% (1)	-	-
	Remission		84% (11)	76.9% (10)	80.8% (21)	69.2% (9)
	Recurrence		15.4% (2)	23.1% (3)	19.2% (5)	30.8% (4)
	Treatment 4	Glucocorticoids	0% (0)	0% (0)	-	-
		Glucocorticoids + methotrexate	0% (0)	0% (0)	-	-
		Conservative treatment	7.7% (1)	15.4% (2)	-	-
		Surgery	7.7% (1)	7.7% (1)	-	-
	Remission		100% (13)	100% (13)	100% (26)	100% (13)
	Recurrence		0% (0)	0% (0)	0% (0)	0% (0)
Side effects	+		-	-	-	69.2% (9)
	-		-	-	-	30.8% (4)
Distribution of combined treatments		Medical treatment	69.2% (9)	76.9% (10)	73.1% (19)	61.5% (8)
		Medical treatment + surgery	30.8% (4)	23.1% (3)	26.9% (7)	15.4% (2)
		Medical/medical + surgery	-	-	-	23.1% (3)

NSAIDs: Non-steroidal anti-inflammatory drug

significant difference was observed between the total durations of the combined treatments (BCM, BCMS, UCM/UCMS, UCM, UCMS). However, in the analysis of unilateral subgroups, patients who received UCMS had significantly longer total remission time (p=0.018) and total follow-up time (p=0.037), and the patients were young (p=0.037) (Table 2-4).

Discussion

Granulomatous mastitis is divided into two main groups depending on the etiological factor: specific or non-specific (idiopathic). The term "idiopathic" is used for cases where a local or systemic etiology affecting the breast is not defined (2). IGM is a rare benign chronic disease of the breast that clinically and radiologically simulates breast carcinoma (1,2). The disease can occur in any quadrant or different quadrants of the unilateral (right or left) breast or it can develop bilaterally. The incidence of BIGM is very rare and has been reported in the literature to vary from 3% (4/152) to 7% (49/720) (6,12). In our study, the prevalence of IGM was 3.03% (13/428) in all granulomatous mastitis and 3.59% (13/362) in IGM; these results are similar to those in the literature.

Skin thickening, distortion, calcification, lymphadenomegaly, irregular focal mass, or diffuse asymmetry can be seen in MMG. However, MMG may not indicate any signs when the breasts are dense. In cases of diffuse disorder or where MMG/USG is insufficient, MRI can be preferred. IGM is frequently seen in premenopausal young patients presenting with signs of breast mass and mastitis. Therefore, the first is examined with USG rather than MMG and MRI. Radiologically, USG can detect inflammation, abscess, tunnel, sinus, and mass size. Also, USG is beneficial for guiding biopsy and during follow-up after treatment. However, none of the radiological methods can clearly distinguish the malignancy (6,13,14). Similar to the literature, USG was the first radiological method preferred in all patients (100%). The additional radiological techniques applied were MMG for patients aged 40 years and over and MRI when USG is insufficient to make a definitive diagnosis.

Table 3. Comparison of bilateral combined treatment methods

		Bilateral medical treatment		Bilateral medical treatment plus surgery		Medical treatment/surgery plus Medical		
		Min.-max.	Mean ± SD/% (n)	Min.-max.	Mean ± SD/% (n)	Min.-max.	Mean ± SD/% (n)	p
Age		27.0-53.0	38.75±10.14	25.0-29.0	27.00±2.83	33.0-39.0	35.67±3.06	0.272[A]
The first side affected	B/R/L		62.5% (5)/12.5% (1)/25% (2)		50% (1)/50% (1)/0% (0)		0% (0)/33.3% (1)/66.7% (2)	0.291χ^2
Synchronous/ metachronous			75% (6)/25% (2)		50% (1)/50% (1)		0% (0)/100% (3)	0.084χ^2
Premenopause/ menopause	+		75% (6)/25% (2)		100% (2)/0% (0)		100% (3)/0% (0)	0.478χ^2
Pregnancy	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Breastfeeding	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Smoking	+/-		25% (2)/75% (6)		0% (0)/100% (2)		0% (0)/100% (3)	0,478x^2
Trauma	+/-		0% (0)/100% (8)		0% (0)/100% (2)		33.3% (1)/66.7% (2)	0.164x^2
OC	+/-		12.5% (1)/87.5% (7)		0% (0)/100% (2)		33.3% (1)/66.7% (2)	0.561χ^2
TBC exposure	-		100% (8)		100% (2)		100% (3)	1.00χ^2
Mass	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Inflammation	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Fistula	+/-/(+/-)		25% (2)/25% (2)/50% (4)		50% (1)/50% (1)/0% (0)		0% (0)/66.7% (2)/33.3% (1)	0.483x^2
Nipple retraction	+/-/(+/-)		12.5% (1)/75% (6)/12.5% (1)		0% (0)/50% (1)/50% (1)		0% (0)/66.7% (2)/33.3% (1)	0.749χ^2
Erythema nodosum	+/-		12.5% (1)/100% (7)		0% (0)/100% (2)		0% (0)/100% (3)	0.713χ^2
Abscess drainage	+/-/(+/-)		62.5% (5)/12.5% (1)/25% (2)		0% (0)/0% (0)/100% (2)		66.7% (2)/0% (0)/33.3% (1)	0.371χ^2
Total treatment duration (months)		3.37-69.90	32.12±26.66	17.50-29.50	23.50±8.49	20.93-53.33	37.51±16.21	0.813[A]
Total remission duration (months)		3.30-63.47	26.46±23.83	51.40-88.93	70.17±26.54	23.47-77.70	49.73±27.16	0.138[A]
Total follow-up duration(months)		9.37-107.77	61.58±38.66	80.90-106.43	93.67±18.06	68.97-115.97	87.24±25.18	0.390[A]

χ^2: Pearson chi-square/Fisher's exact test, [A]: One-Way ANOVA, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-)

Table 4. Comparison of unilateral combined treatment methods

Min.-max.		Unilateral medical treatment		Unilateral medical treatment plus surgery		p
		Mean ± SD-% (n)	Min.-max.	Mean ± SD-% (n)		
Age (year)		27.0-53.0	38.95±9.06	25.0-39.0	30.86±5.18	**0.037[t]**
Premenopause/menopause	+		78.9% (15)/21.1% (4)		100% (7)/0% (0)	0.546[x2]
Breastfeeding	+		100% (19)		100% (9)	1.000[x2]
Lactation	+		100% (19)		100% (9)	1.000[x2]
Smoking	+/-		21.1% (4)/78.9% (15)		0% (0)/100% (7)	0.546[x2]
Trauma	+/-		5.3% (1)/94.7% (18)		14.3% (1)/85.6% (6)	0.474[x2]
OC	+/-		15.8% (3)/84.2% (16)		14.3% (1)/85.7% (6)	1.000[x2]
TBC exposure	-		100% (19)		100% (19)	1.000[x2]
Right/Left			47.4% (9)/52.6% (10)		57.1% (4)/42.9% (3)	1.000[x2]
Size of mass (cm)		1.9-12.0	4.27±2.43	2.6-7.0	3.94±1.49	0.735[M]
Mass	+		100% (19)		100% (7)	1.000[x2]
Inflammation	+		100% (19)		100% (7)	1.000[x2]
Fistula	+/-		42.1% (8)/57.9% (11)		57.1% (4)/42.9% (3)	0.665[x2]
Nipple discharge	+/-		15.8% (3)/84.2% (16)		28.6% (2)/71.4% (5)	0.588[x2]
Erythema nodosum	+/-		10.5% (2)/89.5% (17)		0% (0)/100% (7)	1.000[x2]
Abscess drainage	+/-		73.7% (14)/26.3% (5)		71.4% (5)/28.6% (2)	1.000[x2]
Total treatment duration (months)		0.73-69.9	22.76±24.25	6.33-31.93	15.10±10.99	0.866[M]
Total remission duration (months)		3.3-108.0	41.09±29.54	48.03-170.9	84.66±42.45	0.018[M]
Total Follow-up Duration (months)		9.37-109.07	63.85±36.60	61.13-177.80	99.76±37.59	0.037[t]

X^2: Pearson chi-square/Fisher's exact test, [t]: Independent samples t-test, M: Mann-Whitney U test, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-)

Due to the similarity of signs and symptoms, breast cancers, sarcoidosis, Wegener's granulomatosis, foreign body granulomas, breast infections (bacterial, fungal, parasitic), and breast tuberculosis should be considered in the differential diagnosis (1,2,6,15-17). The diagnosis of BIGM is confirmed by the presence of non-caseating sterile granulomas containing epithelioid histiocytes, giant cells, plasma cells, and eosinophils within the breast lobules on the biopsy (excisional/abscess wall/tru-cut) sample collected from the breast tissue. Tissue biopsies were evaluated with gram staining for bacteria, PAS for fungi, and hematoxylin-eosin for malignancy in the differential diagnosis. Furthermore, foreign bodies may be detected in the histopathological investigation. To exclude TBC, the presence of caseating necrosis in granulomas was tested using EZN staining, PCR, and PPD. For microbiological data, the culture tests of the additional biopsies were performed to confirm the sterility (1,5,6,14-16).

In the literature, there are many hypotheses on the pathophysiology of the disease. The first of these hypotheses is the secretion theory, which includes increased ductal permeability caused by intraductal accumulated secretions or inflammation following ductal epithelial damage. The second is the ethnic hypothesis, based on geography and ethnicity, as the disease occurs in the Mediterranean region and developing Asian countries. The third one is the autoimmune hypothesis, which is accepted due to the high T-lymphocyte count in immunohistochemical studies, its positive response to glucocorticoids or immunosuppressive treatments, and its similarity to diseases such as granulomatous thyroiditis and prostatitis. It is therefore believed that hormonal imbalance, autoimmunity, alpha-1 antitrypsin deficiency, breast trauma, smoking, ductal ectasia, hyperprolactinemia, and the use of OC play a role in the etiology of IGM. However, a definite association has not been demonstrated (2,6,7,12,17-19).

To the best of our knowledge, the incidence of BIGM is quite rare, and the last study we can make a comparison to is from 2016. In this study, patients had a history of parity (100%), lactation (100%), smoking (60%), OC use (10%), exposure to TBC (30%) (EZN negative), and systemic disease (20%), but no patient (0%) had a history of trauma. Of the patients who had a history of systemic disease, one patient had HsT and the other patient had DM. The authors state that there was an association between BIGM and giving birth, breastfeeding, and smoking. However, they did not find an association between BIGM and local trauma or OC use (11). Another study conducted by the same authors in 2021 indicated that the disease is seen in women of childbearing potential who have a history of pregnancy and breastfeeding and that it is not associated with nicotine addiction (6). In our study, the patients had a history of giving birth (100%), breastfeeding (100%), smoking (15.4%), OC use (15.4%), trauma (7.7%), and systemic disease (38.5%). The patients with a history of systemic disease had DM (n=2), HT (n=1), DM plus HT (n=1), and HsT (n=1). None of the patients had a history of hyperprolactinemia, galactorrhea, rheumatologic disease, or exposure to TBC. In this study, we also observed that the incidence of BIGM was higher in patients with a history of pregnancy and breastfeeding.

Although UIGM has been reported in a wide age range (11 to 83 years), it is most commonly seen in the third and fourth decades (2,6,14). The most common symptoms that patients had at presentation to the hospital are local or widespread inflammation accompanied by a mass and redness in the breast. In the literature, the distribution of these symptoms in UIGMs is as follows: 83% mass, 42% abscess, 6.6% erythema nodosum, and 30% fistula (12,18-20). The distribution of these symptoms in the BIGM (n=0) is as follows: 100% mass, 70% inflammation, 90% abscess, and 70% fistula. Eighty percent of the patients (n=10) were premenopausal and the mean age was 38±8.3 years (range: 29 to 52 years) (11). As can be seen, BIGMs were complicated mastitis cases with a higher rate of abscesses and fistulas (8,18). In our study, 84.6% of the patients with BIGM (n=13) were premenopausal and their mean age was 36.23±8.89 years (range: 25 to 53 years). The most common signs in all patients (100%) were breast mass (the mean size of the masses in the right breasts was 4.98±2.65 cm, in the left breasts was 3.38±1.25 cm and the mean unilateral mass size was 4.18±2.19 cm) and inflammation. Patients had in at least one breast 61.6% (bilateral: 23.1%/unilateral: 38.5%) fistula, 92.3% (bilateral: 53.8%/unilateral: 38.5) abscess, 30.8% (bilateral: 7.7%/unilateral: 23.1%) nipple retraction, 7.7% erythema nodosum. In the unilateral evaluation, these rates were lower, with 46.2% fistula, 73.1% abscess, 19.2% nipple retraction, and 7.7% erythema nodosum. However, the incidence of complicated mastitis was high in subjects with BIGM in both bilateral and unilateral analyses.

From the day it was introduced until 1980, aggressive surgical treatment methods were used for treating IGM. After 1980, aggressive surgical treatment methods were replaced by glucocorticoids, methotrexate, colchicine, Imuran(azathioprine), NSAIDs, and conservative treatment methods (2-4,6,7-10,21). Today, the first choice for treating UIGM and BIGM is medical treatment, and surgery is performed in selected resistant cases (12,22,23). Although the disease is considered sterile, drainage (incisional or percutaneous) and empirical antibiotic therapy are recommended in patients with the signs of mastitis and/or abscess, since the disease cannot be differentiated from pyogenic mastitis at the beginning (6,12). In the study, in which 93% of the patients (n=720) had UGM, the distribution of treatment methods preferred was 36% medical, 8% surgery, and 56% combination of medical and surgery. Seventeen patients had disease recurrence (12). In a study conducted in 2016, 100% of patients with BIGM (n=10) received empirical antibiotic therapy and 90% of them underwent abscess drainage. However, all of these patients had disease recurrence. After BCM therapies were administered following recurrence, 90% of the patients achieved remission for 21 months (range, 11 to 26 months). In our study, the distribution of treatment options applied for the patients (n=13) was 61.5% BCM, 15.4% BCMS, and 23.1% BCMS/BCM treatment. The distribution of patients receiving unilateral therapies was 73.1% (19/26) UCM and 26.9% (7/26.9) UCMS. While recurrence (100%) was observed in at least one breast of the patients (n=13) after the first session of treatment, the recurrence rate was 92.3% in the unilateral subgroup (n=26) analysis. After combined therapies, all patients achieved remission. There was no significant difference (p>0.05) between the groups regarding total treatment duration (BCM, BCMS, UCM/UCMS, UCM, UCMS). Since the patients who received UCMS treatment were younger patients that fallen in the baseline section (12-year cross-section) of the study, the total durations of remission (p=0.018) and follow-up (p=0.037) were significantly longer (p=0.037) in the analysis of unilateral subgroups. However, a limitation of the study was that young patients who were resistant to medical treatments preferred surgery.

Study Limitations

Our study has some other limitations. 1) Although our study could not provide strong evidence due to the rarity of BIG patients, limited sample size, and retrospective design, it is one of the most comprehensive studies to date revealing the clinical features of BIGM in the literature. 2) Etiological reasons for preferring surgical treatment in young patients who were resistant to medical treatment was the gray zone of the study.

Conclusion

The clinicoradiological diagnosis of BIGM consisting of complicated mastitis with a high recurrence rate is made as in UIGM. However, a descriptive etiology is excluded with the collection of tissue biopsies from each breast separately for histopathological and microbiological diagnosis. Although there is no significant (p>0.05) difference between the total combined (BCM, BCMS, UCM/UCMS, UCM, UCMS) treatment durations of the patients, the first choice for treating patients with BIGM is medical treatment methods. Surgery can be performed for patients who are resistant to medical treatment.

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