Clinical Characteristics and Treatment Approach of Idiopathic Granulomatous Mastitis

İdiyopatik Granülomatöz Mastitde Klinik Bulgular ve Tedavi Yaklaşımları

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ABSTRACT

Objectives: The purpose of this study was to evaluate the clinical characteristics, treatment approaches, and outcome of the patients with idiopathic granulomatous mastitis (IGM).
Methods: The patients with IGM were reviewed retrospectively from 2011 to 2017. Event free follow up rate was estimated by using Kaplan-Meier analysis, and follow up differences for prognostic factors were compared by using the log-rank test. Multivariate analysis was performed by using Cox-regression method.
Results: There were 69 patients with histologically proven IGM with median age 34 years (range, 21-68 years) at diagnosis. The majority of the symptoms and signs were breast lump, pain, erythema and axillary lymphadenopathy. The most common extramammary finding was eritema nodosum. The most common treatment approaches were only antibiotic or antibiotic plus drainage. The estimated event free follow up rate was 74.7%. It varied according to parity distribution, erythema, extramammary manifestation, and treatment modalities. Cox regression analysis showed that parity distribution, extramammary manifestation and treatment.
Conclusion: This is one of the largest series in a single center. Factors affecting event free follow up rates were parity, erythema, extrammamary manifestations and treatment modalities.

Key Words: Idiopathic granulomatous mastitis, diagnosis, treatment, outcome

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ÖZET

Amaç: Bu çalışmanın amacı, idiyopatik granülomatöz mastit (IGM) tanısı alan hastalardaki klinik bulgular, tedavi yaklaşımları ve sonuçların değerlendirilmesidir.
Yöntem: 2011-2017 yılları arasında IGM tanısı alan hastalar retrospektif olarak incelendi. Olaysız takip oranları Kaplan-Meier analizi ile, prognostik faktörlerdeki farklılıklar da log-rank testi kullanılarak analiz edildi. Multivaryant analiz için Cox-regresyon metodu kullanıldı.
Bulgular: Histopatolojik olarak IGM tanısı alan 69 hasta vardı. Hastaların tanı anındaki median yaşı 34 yıl (21-68 yıl) idi. En sık rastlanan semptom ve bulgular memede kitle, ağrı, eritem ve aksiller lenfadenopatiydi. En sık saptanan meme-dışı bulgu eritema nodozumdu. Tedavi yaklaşımında en çok antibiyotik tedavisi ya da drenaj ile birlikte antibiyotik tedavisi kullanıldığı görüldü. Olaysız takip oranı % 74,7 olarak hesaplandı ve bunun gebelik,eritem varlığı, meme-dışı bulguların varlığı ve tedavi yaklaşımlarına göre değişkenlik gösterdiği görüldü. Cox-regresyon analizinde de gebelik, meme-dışı bulgular ve tedavi seçiminin ön plana çıktığı görüldü.
Sonuç: Bu çalışma tek merkezde yapılan en geniş vaka sayısını içeren serilerden biridir. Olaysız takip oranlarını etkileyen faktörler; gebelik, eritem varlığı, meme-dışı bulguların varlığı ve tedavi yaklaşımları olarak göze çarpmaktadır.

Anahtar Sözcükler: İdiyopatik granülomatöz mastit, tanı, tedavi, sonuçlar

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM), firstly described by Kessler and Wolloch (1), is a rare inflammatory disease of the breast. The most common symptom is a firm unilateral, discrete breast mass. It can be associated with an inflammation of the overlying skin, nipple retraction and even a sinus formation (2). The etiologic causes of the granulomatous inflammation of the breast are infectious (such as Mycobacterium tuberculosis, Blastomycosis, Cryptococcosis, Histoplasmosis, Actinomycosis, Filarial infection or Corynebacterium), autoimmune process (such as Wegener granulomatosis, giant cell arteritis or foreign body reaction), duct ectasia (such as plasma cell mastitis, subareolar granuloma or periductal mastitis), diabetes mellitus, sarcoidosis, fat necrosis and idiopathic (3). Some HLA types, such as HLA-A*10, HLA-*2403, HLA-B*18 and HLA-DR*17 antigens have been reported more frequently in Turkish IGM patients (4). It can look alike breast carcinoma clinically or/and radiologically, IGM may also be associated with breast cancer (2, 3).

Although clinic and radiological examinations including mammography, ultrasonography, magnetic resonance imaging and sonoelastography are very useful in the diagnosis of IGM, biopsy is necessary for definite diagnosis and to exclude the possible breast cancer (2, 3).

Herein, we presented our experience on IGM's clinical characteristics and treatment approach.

MATERIAL and METHODS

Sixty nine patients were enrolled with histologically proven IGM who were treated and followed-up by a surgeon between 2011 and 2017. Core needle biopsy or open surgical biopsy was performed for diagnosis. The patients' epidemiologic and clinic characteristics, microbiologic studies, treatment modalities, complications and follow-up data for each patient were recorded, retrospectively.

If done, radiologic examinations (mammography, ultrasound or/and magnetic resonance imaging) were reevaluated by a radiologist. The results of imaging studies were evaluated using the breast imaging reporting and data system (BIRADS) (5th edition) which was published by American College of Radiology (5).

The pretreatment factors for prognostic significance were age (<40 years and ≥40 years); parity (0, 1-2 and ≥3); the passed since the last pregnancy (pregnant-6 months, >6 months); localization (peripheral, central or mix); and the number of affected quadrant of the breast (localize disease was defined affected 1 or 2 quadrants, advanced disease was defined affected 3 or 4 quadrants). The treatment modalities were wait and see; antibiotic; drainage+antibiotic; and surgery+drainage plus antibiotic. As a retrospective study, ethics committee approval and informed consent were not obtained.

Statistical analyses

Median values were used to analyze demographic features. Relapse and progression were expressed as percentages. The follow up times were recorded. In IGM, the event was defined as recurrence, unresponsiveness to treatment in one month or progression. Event free time is calculated as the time from the diagnosis to final check or event. Event free follow up (EFF) rates were estimated by using Kaplan-Meier analysis, and follow up differences for prognostic factors were compared by using the log-rank test. Multivariate analysis was performed by using Cox-regression method. The p values <0.05 was accepted as significant.

RESULTS

Patients' characteristics

The patients' clinical characteristics were given in Table 1. There were 69 patients with histologically proven IGM with median age 34 years (range, 21-68 years) at diagnosis. Only two patients had bilateral disease (2.8%). Median parity number was 2 (range, 0-7). The affected quadrant(s) of the breast were 43 (1 quadrant), 9 (2 quadrant), 3 (3 quadrant), and 13 (4 quadrant). One patient did not have any active lesion.

The symptoms and signs were breast lump (n: 67, 97%), pain (n: 58, 84%), erythema (n: 40, 58%), ulceration (n: 5, 7%), nipple retraction (n: 7, 10%), axillary lymphadenopathy (n: 29, 42%), skin inflammation (n: 8, 12%) and peaud' orange (n: 1, 1.4%).

Six patients (9%) had extramammary manifestation or disease. There were erythema nodosum (n: 3), xerosis cutis (n: 1), rosacea (n: 1) and dermatitis (n: 1).

Microbiological studies

Microbiological culture were obtained from 51 patients and culture was positive in only two patients (4%) (gram positive coccus, mycobacterium).

Radiologic findings

Radiological breast type A, B, C and D were 2 (3%), 14 (20%), 42 (60%), and 12 (17%), respectively.

Ten patients had mammography. There were focal asymmetrically increased density in 6 patients, diffuse increased density in 3 patients and ill-defined nodular density in one patient. All of the patients had ultrasonography. Heterogeneous hypoechoic lesion with well-defined border in 39 patients (55%), heterogeneous hypoechoic ill-defined lesion with tubular extensions in 25 patients (35.2%), and parenchyma heterogeneous in 5 patients (7%) were determined. In 2 patients (2.8%), ultrasonography was normal.

Fifty-one patients had magnetic resonance imaging. The patients' magnetic resonance findings were in Table 2. On dynamic contrast enhanced MRI, non-mass enhancement (NMEs) alone was seen in 46 (90%) breasts. The most frequent distribution of NMEs was regional in 27 (53%). Enhancement patterns of these lesions were clustered ring (ring like enhanced lesions with smooth margins and related boundaries) in 36 (78%) and heterogeneous in 10 (22%). The time-intensity curves of the dynamic studies showed benign type 1 kinetic curves (persistent enhancement pattern) in the majority of lesions 33 (65%). Type 2 (plateau enhancement pattern) was detected in 18 (35%) while malignant type 3 (washout pattern) was found in none of the lesions.

Table1: The patients' clinical characteristics

	n	%
Age distribution		
<40 years	55	80
≥40 years	14	20
Parity, (range)	2 (0-7)	
Parity distribution		
0	5	7
Pregnant	3	4
1-3	44	64
≥3	17	25
The time since the last pregnancy		
No parity	5	7
Pregnant	3	4
The first year after birth	9	13
>12 months	56	76
Localization		
Central	48	70
Peripheral	21	30
The number of affected quadrant of the breast		
No active lesion	1	1,4
1	43	62
2	9	13
3	3	4
4	13	19.6
Localize disease (1&2)	52	75
Advanced disease (3&4)	16	23.6
Symptoms and signs		
Breast lump	67	97
Pain	58	84
Erythema	40	58
Axillary lymphadenopathy	29	42
Skin inflammation	8	12
Nipple retraction	7	10
Ulceration	5	7
Eryhtema nodosum	3	4
Sinus formation	2	3
Peaud'orange	1	1.4

Treatment modalities

The treatment modalities were wait and watch (n: 3, 4%), only antibiotic (n: 15, 22%), drainage plus antibiotic (n: 45, 65%), and drainage + surgery + antibiotic (n: 6, 9%). Only three patients in group drainage plus antibiotic were administered topical steroid. In the patients with localize disease, there were wait and watch (n: 3), only antibiotic (n: 12), drainage+antibiotic (n: 31), and drainage+surgery+antibiotic (n: 6). However, there were only antibiotic (n:3) and drainage plus antibiotic (n: 13) in the patients with advanced disease. There was no statistically significant difference between the local and advanced disease groups in terms of treatment approach (p>0.05).

Event free follow up analysis

At a median follow-up of 23 months (range, 1-114 months), 57 patients were disease free. The estimated EFF rate was 74.7%.The EFF rates varied according to parity distribution (p=0.006), erythema (p=0.006), extramammary manifestation (p=0.007), and treatment modalities (p=0.004) (Fig 1) (Table 3). Cox regression analysis showed that parity distribution, extramammary manifestation and treatment (Table 4).

Table 2: The magnetic resonance imaging findings

	n (%)
Magnetic resonance imaging findings	
Mass	5 (10%)
Non-mass enhancement	46 (90%)
Architectural distortion	3 (6%)
Fistula	18 (35%)
Skin involvement	17 (33%)
Retroaereolar involvement	25 (49%)
Ductal dilatation	23 (45%)
Axillary lympadenopathy	33 (65%)
Patterns and distribution of non-mass enhancement	
Non-mass enhancement	46 (90%)
Non-mass enhancement patterns	
Clustered ring	36 (78%)
Heterogeneous	10 (22%)
Distribution	
Lineer	3 (6%)
Segmental	4 (8%)
Regional	27 (53%)
Single lesion	5 (10%)
Diffuse multiple	12 (23%)
T1A-T2A	
T1 WI hypointense-T2 WI hyperintense	26 (51%)
T1 WI intermediate-T2 WI hyperintense	8 (16%)
T1 WI hypointense-T2 WI heterogeneous hyperintense	4 (8%)
T1 WI heterogeneous hypointense-T2 WI heterogeneous hyperintense	13 (25%)
Type of enhancement curve	
Type 1	33 (65%)
Type 2	18 (35%)
DWI	
Restricted	49 (96%)
Unaffected	2 (4%)
Background parenchymal enhancement	
Positive	11 (21.5%)
Negative	40 (78.5%)

WI: weighted images, DWI: diffusion-weighted imaging

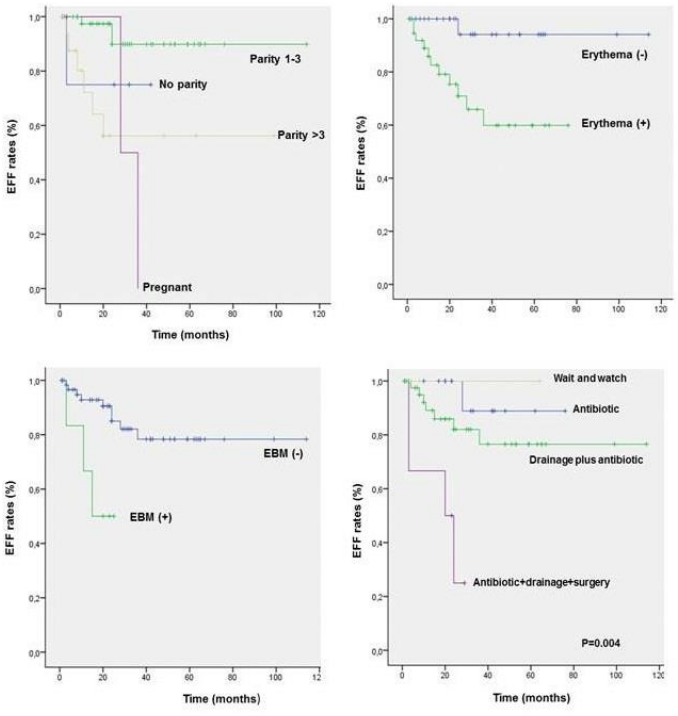

Figure1: Factors affecting event free follow-up rates

Table 3: Results of univariate analysis for EFF rates

Variables	Patients n	EFF EFF	p
Age distribution			0.29
<40 years	55	71	
≥40 years	14	90	
Parity distribution, [a]			0.006
No parity	5	75	
Pregnant	3	0	
1-3	44	90	
>4	17	56	
The time since the last pregnancy			0.1
No parity	5	75	
Pregnant	3	0	
The first year after the last birth	8	100	
>12 months	53	79	
Localization			0.55
Central	48	74.7	
Peripheral	21	76	
Symptom and signs			
Pain			0.193
Negative	11	100	
Positive	58	72	
Erythema			0.006
Negative	29	94.1	
Positive	40	60	
Mass			-
Negative	2	-	
Positive	67	73.5	
Skin inflammation			0.79
Negative	61	76	
Positive	8	68.6	
Ulceration			0.72
Negative	64	74.6	
Positive	5	80	
Nipple retraction			0.44
Negative	62	76.1	
Positive	7	7	
Axillary lymphadenopathy			0.95
Negative	40	71.8	
Positive	29	80.3	
The number of affected quadrant of the breast			0.7
Localize disease (1&2)	52	79.4	
Advanced disease (3&4)	16	64.2	
Extramammary manifestation			0.007
Negative	63	78.4	
Positive	6	20.4	
Treatment, [b]			0.004
Wait and watch	3	100	
Antibiotic	15	89	
Antibiotic+drainage	45	76.5	
Antibiotic+drainage+surgery	6	25	

EFF: Event free follow-up
a: The group of the parity 1-3 &>3, p=0.001
b. The group of the antibiotic &antibiotic+drainage, p=0.27;
The group of the antibiotic &antibiotic+drainage+surgery, p=0.001;
The group of the antibiotic+drainage&antibiotic+drainage+surgery, p=0.003

Table 4: Multivariate analysis of 69 patients with IGM

	B	SE	P	ODD ratio	95%CI	
Parity	0.905	0.298	0.002	2.472	1.379	4.433
Extramammary manifestation	1.783	0.735	0.015	5.95	1.409	25.124
Treatment	1.747	0.598	0.004	5.738	1.776	18.539

IGM: Idiopathic granulomatous mastitis

Characteristics of patients with failed treatment

The disease was recurred in 4patients; the others were patients who did not respond to treatment during the first month of treatment. The treatment failure occurred in 7 of 45 patient performed antibiotic plus drainage (15.5%), in 4 of 6 patients performed antibiotic + drainage + surgery (66.6%) and one of 15 treated only antibiotic (6.6%). The treatment modalities were antibiotic plus drainage in 7 patients (58.3%), antibiotic + drainage + surgery in 4 patients (33.4%) and only antibiotic in one patient (8.3%). In two patients who developed recurrence disease, it recurred at pregnancy. One patient developed relapse at a different localization at the 11thmonth. Nothing was found in the etiology of relapse at the 4th patient. Erythema nodosum was detected at the 7th months of the diagnosis in a patient who did not respond to the treatment. Whilst, no feature were found to explain why the treatment failed in the others.

DISCUSSION

Different etiological factors including infection, autoimmune process, duct ectasis, diabetes mellitus, sarcoidosis, and fat necrosis are known to cause granulomatous inflammation in the breast. However, the majority of the cases' cause is idiopathic. Although rare, the highest number of cases has been reported from some countries such as Turkey, China, South Korea, United States and Saudi Arabia (3).

The majority presenting symptoms and signs are palpable mass, breast pain and swelling, erythema and purulent drainage (2, 6, 7). Also, erythema of the overlying skin, peaud' orange, ulcerated areas and sinus tracts or fistulae, nipple retraction, and axillary lymphadenopathy may be seen. In our study, the presenting symptoms and signs were breast lump, pain, erythema, ulceration, nipple retraction, axillary lymphadenopathy, skin inflammation, peaud' orange and sinus formation. Another symptom or sign of IGM is erythema nodosum. Erythema nodosum is an important finding that should be noted in the symptoms or findings (6, 8, 9). Mahmodlou and his colleagues (6) reported that only 2 of 48 patients had erythema nodosum (4.1%). In our study, 3 of 69 patients had erythema nodosum (4%). Also, three patients had xerosis cutis, rosacea and dermatitis.

Radiological imaging methods including mammography, ultrasound examination and magnetic resonance imaging are the first evaluation methods in the diagnosis of IGM. Although masses (multiple, small, and ill-defined) or a large focal asymmetric density with small and well-defined masses or skin thickening can be seen. Also, calcification, speculation or changes involving the skin or nipple are usually not expected (10, 11). In our study, focal asymmetrically increased density (n: 6), diffuse increased density (n: 3) and ill-defined nodular density (n: 1) in mammography. No calcification was observed in any of our patients. Ultrasound examination shows large, irregular hypoechoic mass with multiple tubular extensions; lobulated or irregular hypoechoic mass; parenchymal distortion with acoustic shadowing and no discrete mass, axillary adenopathy and skin thickening.[11, 12] In our study, heterogeneous hypoechoic lesion with well-defined border (55%), heterogeneous hypoechoic ill-defined lesion with tubular extensions, (35.2%), and parenchymal heterogeneity (7%) were detected. But ultrasound examination was normal in 2 patients.

The MRI findings of IGM have a wide spectrum. Also, no characteristic findings of MRI have been reported yet. Generally, common findings on MRI are masses with rim enhancement or clustered-ring non-mass lesions with segmental distribution. Ductal ectasia and periductal enhancement were commonly accompanying; these findings and kinetic analysis are valuable findings for distinguishing IGM from invasive cancer (14, 15).

In our study, on dynamic contrast enhanced MRI, non-mass enhancement (NMEs) alone was seen in 46 (90%) breasts. The most frequent distribution of NMEs was regional in 27 (53%). Enhancement patterns of these lesions were clustered ring (ring like enhanced lesions with smooth margins and related boundaries) in 36 (78%) and heterogeneous in 10 (22%). The time-intensity curves of the dynamic studies showed benign type 1 kinetic curves (persistent enhancement pattern) in the majority of lesions 33 (65%). Type 2 curve (plateau enhancement pattern) was detected in 18 (35%) while malignant type 3 curve (washout pattern) was found in none of the lesions.

An ideal treatment approach has not yet been established in the treatment of IGM. Benson and Dumitru (2) suggest a treatment approach in their review article. Observation or surgical excisions with free margin are recommended in patients with localized and small lesion. If the treatment is unsuccessful in patients undergoing surgery, steroid or methotrexate therapy may be applied. Steroid or methotrexate can be used in patients with large, diffuse and complicated lesions. If this treatment approach fails in this group, surgery is recommended. In patients with borderline lesion, surgical excision or steroid/methotrexate therapy may be preferred by the patient.

Antibiotics and steroid treatment have a special place in medical treatment. Antibiotics should always be used in patients with infection or abscess signs. Commonly recommended antibiotics are flucloxacillin, co-amoxiclav and doxycycline (2). Another medical treatment option is steroids despite possible side effects. Different steroid application protocols have provided satisfactory results (2, 16). Akin and colleagues (8) reported the successful results of steroid treatment in IGM patients with erythema nodosa.

In the IGM patients with abscess or complications, basic surgical principles such as drainage and / or debridement should be applied. But, major surgery including wide local excision with negative margins or mastectomy may be preferred in selected patients. In our study, most of the treatment options were antibiotics or antibiotics plus drainage. Only three patients were observed andantibiotic+drainage+surgery were performed in 6 patients. The surgical procedure was wide local excision.

The event was developed in 12 patients. The ratio of EFF calculated by Kaplan-Meier analysis was 74.7%. The EFF rates varied according to parity distribution, erythema, extramammary manifestation, and treatment modalities. Cox regression analysis showed that parity distribution, extramammary manifestation, erythema and treatment. When the cases with event were examined the disease recurred in four patients. Two patients developed recurrence during pregnancy. One patient developed relapse at a different localization at the 11thmonth. No significant feature was found in a patient developing relapse. The others were patients who did not respond to treatment during the first month of treatment. Erythema nodosum was detected at the 7th month of the diagnosis in a patient who did not respond to the treatment. No features were found to explain why it failed in the others. The treatment failure occurred in 7 of 45 patient performed antibiotic plus drainage (15.5%), in 4 of 6 patients performed antibiotic + drainage + surgery (66.6%) and one of 15 treated only antibiotic (6.6%).

In conclusion, IGM is a rare entity with unknown etiology. Although there is a predisposition in some races no relationship among the race and etiological factor had been defined yet. Just like etiology, also there is no consensus in treatment strategies. In this era, there are more prospective studies needed to explain the etiopathogenesis and to decide the point target therapy.

Conflict of interest

No conflict of interest was declared by the authors.

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