BREAST SURGERY



Factors related to recurrence of idiopathic granulomatous mastitis: what do we learn from a multicentre study?

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory disease of the breast. It was first defined by Kessler and Wolloch in 1972.¹ It typically affects young women between 17 and 42 years of age within the reproductive and post-child-bearing period. IGM comprises 24% of all inflammatory diseases of the breast.²

The annual prevalence and incidence of IGM have been reported as 2.4 per 100 000 women and 0.37%, respectively.^{3,4} Although its prevalence in Turkey has not been clearly established, it is thought to be higher than in the USA.⁵

Although IGM is a benign disease, it mimics breast cancer, both clinically and radiologically.⁶ As IGM has the same radiological

Abstract

Background: Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory disease of the breast with unknown aetiology. Its treatment is controversial and the recurrence rate is high. The objectives of this study were to examine the demographic, sociocultural and clinical characteristics observed among a large cohort of IGM patients from Turkey and to identify factors related to the recurrence of IGM.

Methods: The study was designed as a multicentre retrospective study including 22 breast centres in Turkey. A total of 720 IGM patients are included in the study. Patient data were obtained from the patient's files and electronic records based on the study protocol. Patients' demographic, clinical, radiological, treatment and recurrence of IGM related characteristics were recorded.

Results: Our results revealed a statistically significant association between IGM recurrence and history of pregnancy, breastfeeding, breast infection and smoking (P < 0.05). Having a chronic systematic disease, oral contraceptive, analgesic and herbal medicine consumptions, treatment choice, education, place of birth and current residence were not found to be associated with IGM recurrence (P > 0.05).

Conclusion: Our findings show that history of pregnancy, breastfeeding, breast infection and smoking were the risk factors for IGM recurrence. As current treatment methods did not affect IGM recurrence, recurrence-related factors, such as breast infection and smoking, should be considered to eliminate while focusing on less invasive local treatment research.

characteristics with breast cancer, dilemmas are observed in the diagnosis.⁷ Precise diagnosis may only be confirmed histopathologically in IGM.^{8,9}

The treatment of IGM is still a debate. Currently, there is no universally accepted treatment strategy. Local and systemic corticosteroids and antibiotics are the most frequently used agents in the medical treatment. However, successful results have been reported with agents, such as methotrexate, azathioprine, glucocorticoids, bromocriptine and colchicine.^{10–12} Surgical treatment of IGM includes abscess drainage, local and wide excisions, or mastectomy. Better outcomes have been reported with steroid addition to the surgical treatment.¹³

The aetiology of IGM is not fully understood. However, autoimmune diseases, hormone irregularities, local immune response to trauma, local irritants, undetected organisms, viruses, hyperprolactinemia, diabetes, α -1-antitrypsin deficiency, smoking, ductal ectasis and oral contraceptive use have been blamed as the aetiology.¹⁴ Additionally, sarcoidosis, tuberculosis, foreign substances and corynebacterial infections have been blamed for the aetiology.¹⁵

Recurrence may be observed despite broad surgical excision in IGM. The IGM recurrence rate varies between 5% and 50% according to the literature.^{16–18} Post-excision recurrence may be as high as 50%.5 It is important to know the factors affecting recurrence as much as the aetiological factors in the fight against IGM. Analysing the effects of demographic and clinical characteristics along with the aetiological factors on the IGM recurrence may contribute to the decrease in post-treatment recurrence. Therefore, determination of IGM-related aetiological, clinical and epidemiological factors is required. Furthermore, knowing the relationship between these factors and the recurrence may increase the success rates of the treatment. Although the aetiological, epidemiological and clinical characteristics have been evaluated in previous studies, the effects of these factors on the IGM recurrence have been poorly analysed. Furthermore, the sample sizes of these studies were limited, as IGM is a rare disease. Although IGM is a chronic and recurrent disease, there is not much knowledge regarding the IGM recurrence and the relationship of the chosen initial treatment. The objectives of this study were to examine the demographic, sociocultural and clinical characteristics observed among a large cohort of IGM patients from Turkey and to identify factors related to the recurrence of IGM.

Materials and methods

Our study was designed as a multicentric retrospective study, involving 22 breast centres in Turkey. The data of 720 patients who had the treatment of IGM between January 2011 and March 2016 were included in the study. Patient data were retrospectively obtained by recording the data in patients' files and electronic records based on the protocol created initially for this study. Patients' demographic, clinical, radiological, treatment and recurrence of IGM-related characteristics were recorded. Only the patients who were histopathologically diagnosed with IGM were included in this study. Exclusion criteria included male patients, patients with breast carcinoma coexisted with IGM and non-IGM patients. Patients with tuberculous mastitis were not included in the study. History of pulmonary tuberculosis, evidence of histologically tuberculous mastitis, positive staining with Ziehl-Neelsen or acid-fast or positive tissue cultures and chest X-ray findings consistent with previous tuberculosis findings with positive tuberculin test were excluded in this study. The return of a sign, symptom or disease after a remission was accepted as recurrence. While there were no co-morbidities in 631 patients, various co-morbidities were seen in 89 patients. The definition of a city is a place with a population more than 100 000 habitants and has better life conditions with a better healthcare accessibility; town and village have less population with a limited source of healthcare facilities. Previously diagnosed diseases were defined as chronic diseases, such as hypertension, autoimmune disease and diabetes, and patients were under the appropriate care. This study is registered at Clinicaltrials.gov by the number ID NCT02667132.

Statistical analysis

Continuous and categorical variable differences between the recurrence and no recurrence groups were analysed by *t*-test and chisquare test, respectively. *P*-values <0.05 were considered as statistically significant. All statistical analyses were conducted by SAS/STAT version 9.3 (SAS Institute, Inc, Cary, NC, USA).

Results

A total of 720 IGM patients are included in the study mostly residing in a city. Patient characteristics enrolled in the study are shown in Table 1. The median age was 36 years (32–42). Median follow-up was 16 (8, 33) months. A great majority of patients reported having given birth and breastfeed. A quarter of the patients had a history of smoking; however, the majority of them did not have any chronic diseases and chronic medication use. Breast infection (30%) was more common than systemic infection (11%) or lactation mastitis (18%). The most common symptom was a mass with other symptoms in the breast in 83% (n = 587) of patients, but the minority (7%, n = 50) of patients had only erythema or fistula (Table 2). On physical examination, 75% of women had palpable mass (n = 538). Our findings showed that IGM often located at upper left quadrant (28%, n = 202) and only 5% of the cases were bilateral (Table 2). While 36% (n = 258) of patients received only medical treatment, 8% (n = 60)

Table 1 Patient characteristics enrolled in the study

	Percentage	<i>n</i> (total patients, <i>n</i> = 720)
Median age (25%, 75%) Median follow-up (months) (25%, 75%)		36 (32, 42) 16 (8, 33)
Patient's place of residence City	88	626
Town	9	66
Village	3	21
Education	Ũ	21
Primary school	42	257
High school	36	218
University	12	76
None	10	58
Ever given birth	92	662
Ever breast fed	85	612
Oral contraceptive	13	90
Smoking Chronic diseases	24	172
None	88	632
Hypertension	4	29
Autoimmune disease	3	23
Other	3	21
Diabetes	2	14
Coronary artery disease	0.4	3
Infection		
Breast infection	30	216
Lactation mastitis	18	130
Systemic bacterial infection history	11	81
Medication use		
None	85	613
Others	10	71
Pain medicine	4	30
Herbal medicine	1	6

Systemic bacterial infection: bronchopneumonia, urinary system infections and puerperal infections.

Table 2	Symptom	and physical	examination,	and lesion	localization
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	Percentage	<i>n</i> (total patients, <i>n</i> = 720)
Symptom		
Mass	83	587
Pain	10	72
Other	7	50
Physical examination		
Palpable mass	75	538
Abscess	42	302
Fistula	30	215
Axillary palpable	7	50
lymph node		
Lesion localization		
Left upper quadrant	28	202
Left lower quadrant	9	67
Right upper quadrant	23	166
Right lower quadrant	12	83
Central	13	90
Multiple quadrants	15	112

received only surgical treatment. The combination of surgical and medical treatment was administered to the majority of the patients (56%, n = 398). The most frequent surgical treatment was wide local excision with 69% (n = 323) followed by abscess drainage in 29% (n = 137) and mastectomy in 1.3% (n = 6) (Table 3). Oral steroids were the first choice for medical treatment (39%, n = 253) followed by antibiotics in 37% (n = 240) and the combination of steroid and antibiotics were given to 13% (n = 87) of the patients. Methotrexate was given to only 1% (n = 5) of the patients. Ultrasound, mammography and magnetic resonance imaging were used in 95% (n = 85),⁶

Table 3 G	Granulomatous	mastitis-related	clinical	characteristics
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	Percentage	<i>n</i> (total patients, <i>n</i> = 720)
Unilateral Bilateral Pathological diagnosis	93 7	671 49
Tru-cut	62	437
Post-operative pathology	20	142
Excisional	7	52
Incisional	7	48
FNAB	4	30
Treatment		
Only medical	36	258
Surgery then medical	33	234
Medical then surgery	23	164
Only surgery	8	60
Medical treatment		
Antibiotic	37	240
Steroid	39	253
Steroid + antibiotic	13	87
Others	9	57
Antituberculosis therapy	2	12
Methotrexate	1	5
Surgical treatment	20	222
Wide local excision	69	323
Only abscess drainage	29	137
Mastectomy	1.3	6
Recurrence	17 3	122 22
Relapse after recurrence therapy	3	22
FNAB, fine-needle aspiration bio	psy.	

36% (n = 258) and 32% (n = 228) of the patients, respectively, and 67% (n = 300) of cases were scored as BIRADS 3.

The overall incidence rate of the first recurrence was 17% (n = 122). IGM re-recurrence after treatment of patients was 3% (n = 22). Our results revealed that there are statistically significant associations between IGM recurrence and pregnancy, breastfeeding, smoking and history of breast infection (P < 0.05). On the other hand, using an oral contraceptive, chronic medication use, receiving various IGM treatment methods, education, chronic diseases, place of birth and place of current residence were not found to be associated with IGM recurrence (P > 0.05) (Table 4).

Discussion

IGM is a rare inflammatory disease of the breast. It generally affects young women in their reproductive ages.¹ The pathophysiology of IGM is not clearly understood. However, the onset of some chemical reactions with oral contraceptive intake, infectious processes and autoimmunity are considered to be involved.¹⁹

 Table 4 Comparison of demographic and clinical characteristics, and

 treatment regimens between patient with and without IGM recurrence

Demographic	IGM recurrence		<i>P</i> -value
	No	Yes	
	(n = 598)	(<i>n</i> = 122)	
	00 (00 40)	05 (00 44)	0.40
Median age (25%, 75%) Patient's place of residence, % (<i>n</i>)	36 (32, 42)	35 (32, 41)	0.42 0.11
Village	3 (20)	1 (1)	0.11
Town	9 (51)	13 (15)	
City	88 (523)	87 (103)	
Education, % (<i>n</i>)			0.83
Primary school	42 (209)	45 (48)	
High school	36 (181)	35 (37)	
University None	9 (47) 13 (65)	10 (11) 10 (11)	
Patient characteristics, % (<i>n</i>)	13 (05)	10(11)	
Pregnancy	91 (542)	98 (120)	0.0008
Breast feeding	84 (501)	91 (111)	0.03
Smoking	22 (132)	33 (40)	0.01
Oral contraceptive	12 (74)	13 (16)	0.80
Medication use, % (<i>n</i>)	/		0.7
None	85 (508)	86 (105)	
Others Pain medicine	10 (58) 5 (27)	11 (13) 2 (3)	
Herbal medicine	5 (27) 1 (5)	2 (3) 1 (1)	
Systemic bacterial infection	12 (74)	6 (7)	0.02
history, % (n)	(, .,	0 (//	0.02
Breast infection, % (n)	28 (170)	38 (46)	0.045
Chronic diseases, % (<i>n</i>)			0.52
None	88 (527)	85 (104)	
Hypertension	4 (24)	4 (5)	
Autoimmune disease Other	3 (15) 3 (18)	5 (6) 2 (3)	
Diabetes	1.7 (10)	2 (3) 3 (4)	
Coronary artery disease	0.5 (3)	0 (0)	
Treatment, % (n)	,	- (-)	0.14
Only medical	37 (221)	30 (37)	0.14
Only surgery	8 (48)	10 (12)	0.53
Medical then surgery	22 (130)	28 (34)	0.15
Surgery then medical	33 (195)	32 (39)	0.85
IGM, idiopathic granulomatous mastit	is.		

Although the possible aetiological factors of IGM have not been certainly defined, some factors are believed to be effective, which include autoimmune diseases, undetected microorganisms, hyperprolactinaemia, diabetes and oral contraceptive use.¹⁴ However, the exact factors have not been established yet. In addition to the clinical characteristics of the disease, defining the relation of epidemiological factors with IGM may be important in the prevention.

The studies of Aghajanzadeh *et al.* (n = 206),¹⁸ Al-Khaffaf *et al.* (n = 133),²⁰ Korkut *et al.* (n = 93),²¹ Akcan *et al.* $(n = 74)^{13}$ and Karanlik *et al.* $(n = 60)^{17}$ with rather large series in the literature were those in which some demographic characteristics could be related to IGM. However, as far as our knowledge, our study has the largest number with 720 IGM patients comparing the effects of epidemiological–demographic–clinical factors on recurrence.

Various studies have reported an effect of ethnic origin and geographic region on the IGM prevalence.^{3,22} The prevalence of IGM has been reported to be high in Turkey, Asia, and Far Eastern countries.^{13,17,21,23} In our study, all participants except six foreigners were Turkish. We observed different prevalences in seven different geographic regions of Turkey. This finding indicates that IGM may be observed in different frequencies within the same country as well. IGM generally affects young women between 17 and 42 years of age. The median age observed in our study was compatible with the literature.^{17,18,21} However, IGM may be observed in advanced ages such as 65 or 83 years as well.²⁴ In agreement with a previous report,²⁵ no significant difference was observed between the recurrence and nonrecurrence groups according to the mean age in our study.

Although possible effects of antipsychotic drugs and drugs increasing the prolactin level such as risperidone on IGM have been demonstrated,²⁶ we did not observe any relationship between pain relievers, herbal, antihypertensive or antidiabetic medications and IGM or IGM recurrence.

The relationship between living environment and IGM is not well studied. In our study, 88% of the patients resided in a city. No relation was observed between the region of birth and place of living with the IGM recurrence. The findings observed in our study were found to be compatible with those in the literature.²⁷ In our study, the educational statuses of the patients were mostly primary school, which was followed by high school. No significant difference was observed between the educational status and the IGM recurrence. In the study of Karanlik *et al.*¹⁷ investigating the efficacy of steroids plus surgery in IGM, no significant difference was observed between the educational status and recurrence however, the relation between the educational status and recurrence has not been reported.

Although a possible connection between pregnancy, lactation and IGM recurrence has been reported, their role in IGM pathophysiology is not clear. Secretions, hormonal changes and inflammation during pregnancy and lactation may be effective in the pathophysiology of IGM. Localized autoimmune response against fat- and protein-rich secretions may underly the mechanism of prolactin in IGM pathogenesis.^{26,28–30} Furthermore, prolactin has been demonstrated to cause granulomatous lesions, immune response and non-caseating granulomas in both physiological and pathological actions.³¹ The incidence of prolactinoma among patients with IGM has been reported as 60–100/1 000 000.³² Furthermore, a high prolactin level

has been related to IGM recurrence.¹⁸ In one study, a history of pregnancy and lactating was observed in all patients with IGM except for two among 43 patients.²⁵ In another study, granulomatous mastitis has been reported to be generally observed within several years following delivery.³³ In the study of Al-Khaffaf *et al.*,²⁰ lactating was suggested to be in the history of patients with long-term IGM. Evaluation of patients with regard to the prolactin level and hypophysis adenoma is recommended in granulomatous mastitis.²⁸ The findings observed in our study were found to be compatible with those in the literature.

Smoking is considered to be one of the possible aetiological factors for IGM with no definite conclusion.^{13,20,23} Our results suggested a significant relationship between smoking and IGM recurrence.

As oral contraceptives increase breast secretion, they are potential aetiological factors for IGM. Some studies demonstrate oral contraceptive use among patients with IGM as much as 42.1%. However, no precise relationship has been demonstrated between oral contraceptive use and IGM.²³ In our study, the oral contraceptive use was found to be 13% and no significant relationship was found with the IGM recurrence.

The hypothesis that autoimmunity may cause IGM has long been considered. The good response of IGM to steroid and immunosuppressive agents, the T lymphocyte dominance in immunohistochemical studies and the similarity of granulomatous mastitis to other autoimmune diseases, such as granulomatous thyroiditis and granulomatous prostatitis, form the basis for this theory. However, due to the absence of immunological abnormalities in some patients with granulomatous mastitis, this hypothesis has not been completely confirmed. The recurrence observed despite the immunosuppressive and steroid treatment in some of the patients with IGM has not rendered autoimmunity alone to be responsible in the aetiology.¹³ Furthermore, there is no sufficient evidence on the relation between autoimmunity and granulomatous mastitis. The role of autoimmune factors in the aetiology of IGM was not demonstrated in the study of Altintoprak et al.¹⁴ In our study, autoimmune diseases were observed in only 3% of the patients with IGM. No relationship was observed between the IGM recurrence and autoimmune diseases considered within the group of chronic diseases.

There is a possible relationship between microbiological agents and granulomatous mastitis. Corynebacterium has particularly been blamed in the aetiology of granulomatous mastitis. Corynebacterium was first encountered in 34 of 68 patients with histopathologically diagnosed granulomatous mastitis by Taylor et al.³⁴ However, as Corynebacterium was not isolated from all patients and its role in the aetiology of granulomatous mastitis is not yet clear. In our study, 32% of the patients had breast infections caused by different bacterial agents. A significant relationship was found between breast infection and the IGM recurrence. The infections observed in the patients were not the ones that were diagnosed at the time of the diagnosis of GM. These infections were in the history of the patients. In patients with a history of systemic bacterial infection, a significant relationship was observed between the IGM recurrence and systemic bacterial infection as well.

No correlation is observed between treatment methods and IGM recurrence in our study. Treatment choice and sequence of IGM is still debated. Currently, there is no universally accepted treatment strategy.¹³ Systemic corticosteroids and antibiotics are the most frequently used agents in the medical treatment of IGM. However, successful results have been reported with some agents, such as methotrexate, azathioprine, glucocorticoids, bromocriptine and colchicine¹² or combination with steroids.¹⁰ There are studies reporting lower recurrence rates with broad surgical resection,¹⁹ while others reporting an increased recurrence rate with surgical treatments.

There are certain limitations of our study: one of them was a short duration of patient follow-up; longer follow-up is needed to find out actual recurrence rate. As there were no enough records, the interval between the breastfeeding and the onset of IGM in our study was not evaluated. Collection data retrospectively is another limitation of the study; there is no universal approach to diagnosis and treatment of IGM among the study centres.

Conclusion

Our findings indicate that history of pregnancy, breastfeeding, breast infection and smoking are risk factors for IGM recurrence. As treatment methods examined in this study did not affect IGM recurrence, future research should focus on less invasive local treatment options and eliminate factors, such as breast infection and smoking.

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