Scoring Idiopathic Granulomatous Mastitis: An Effective System for Predicting Recurrence?

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ABSTRACT

Objective: Idiopathic granulomatous mastitis is a breast disease without a definitive etiology. There are no definitive classifications, scoring systems or certitudes. The aim of this study is to define the factors related to the recurrence and design a scoring system.

Material and Methods: Patients who were admitted to the general surgery department with symptoms of granulomatous mastitis were evaluated by ultrasonography and underwent antibiotic therapy. Granulomatous mastitis is diagnosed by core biopsy and treated with steroid therapy. Patients without improvement underwent surgery and were included in the study. In total, 53 patients were included in the study. There were 8 recurrent cases. Factors related with recurrences were defined.

Results: Number of births over 2, duration of lactation more than 18 months, body mass index greater than 31, having fistula in physical examination, abscess collection in ultrasonographic examination, and luminal inflammation score over 2 were scored as 1. Severity score in recurrent cases were 5.1±0.6 whereas 1.9±1.0 in nonrecurrent cases.

Conclusion: Granulomatous mastitis score is a tool targeted at predicting the risk of recurrences. The patients with these factors are more prone for recurrences.

Keywords: Granulomatous mastitis, recurrence, risk factors, surgery


Introduction

Idiopathic granulomatous mastitis (IGM) is a rarely seen inflammatory breast disease without a clearly elucidated etiology. The etiological factors underlying this disease are currently unclear, although a localized autoimmune inflammatory response to retained and extravasated fat- and protein-rich (milk) secretions in the duct has been implicated in its pathogenesis (1). Pregnancy, parity and lactation are considered as risk factors in the pathogenesis of IGM (2-4). Usual presentations of IGM are breast mass, sinus formations and abscesses (1, 2). Entities that should be considered in the differential diagnosis of IGM are malignancies, lactation mastitis, sarcoidosis and tuberculosis (5). The diagnosis of IGM requires a multidisciplinary approach, incorporating clinical, radiological, microbiological and pathological findings.

The best practices for the treatment of IGM are controversial. Conservative treatment such as the use of antibiotics or corticosteroids, or wide excision of the affected tissue have been utilized for treatment (6, 7). Currently, there is no consensus for an ideal way to match a treatment modality to a patient. The current approach to IGM treatment consists of short-term antibiotics, followed by histological confirmation with a core needle biopsy. Following pathological confirmation, the decision to proceed with steroid therapy and/or surgical excision is then left to the clinician (8). The decision criteria for steroid treatment, dose of steroid or the duration of steroid treatment are uncertain. Since successful treatment of IGM is considered to be healing of the current disease, with no recurrences in patient follow-up, the lack of an objective, reproducible severity score for IGM makes it harder for the clinician to stratify patients according to recurrence risk and make an informed decision on the appropriate treatment modality.

In this study, we aimed to develop a combined clinical and histological scoring system to determine the severity of IGM that would assist the clinician in determining the recurrence risk based on factors that were implicated in a higher risk of disease recurrence.
Material and Methods

This study was approved by local ethic committee. Patient information was collected from the hospital database and pathology reports. As being a retrospective study, inform consent was not received from the patients.

Diagnosis and patient selection

A total of 110 patients admitted to our surgery department between January, 2008 and January, 2014 for mastitis, who were then confirmed histologically as IGM, were included in this retrospective study. The study was approved by local ethics committee. Our study method incorporated a multidisciplinary approach in elucidating suspected risk factors for IGM. Hospital records of histologically confirmed IGM patients were reviewed and data on clinical and imaging features were collected. Pathological specimens were re-examined. In our center, patients referred to the Department of General Surgery with mastitis were evaluated in order to differentiate other possible causes. In the case of an ongoing sinus discharge, special stains (Gram, Ziehl-Neelsen, periodic acid Schiff) were used to identify possible organisms in the discharge fluid. Ampicillim-sulbactam (2x1g P.O.) was given to all patients for 10 days. In cases where clinical improvement was absent or minimal, a core biopsy was obtained for the diagnosis of IGM. Patients diagnosed as IGM then underwent corticosteroid treatment (Methylprednisolone (Prednol, Mustafa Nevzat, İstanbul, Turkey)) (30mg/day) for 3 months. The dose of steroid was obtained from the previous studies (1, 3, 7). At the end of the treatment, the mean age of the patients was 38.6±8.4 (23-61). There were 8 recurrences (%12.6) in our study, who underwent subsequent re-excision of affected tissue. None of the patients in our study had Sjögren’s syndrome or hyperprolactinemia. In order to determine the risk factors, we compared the patients with and without recurrences. Contraception usage, parity, age of first birth, affected breast (left or right), bilateral disease, bra-wearing habits or smoking didn’t show any significant difference between two groups (p>0.05). The existence of hyperemia or breast pain was again not significant (p>0.05). The ultrasonographic mean diameters of the breast lesions in two groups or multifocality were also not statistically different (p>0.05).

Severity score factor estimation:

Recent studies about IGM were consulted in order to identify suspected risk factors for disease recurrence (9-14). Information about hyper-prolactinemia, coexisting Sjögren’s syndrome, length of breast feeding period, contraception usage, parity, age at first birth, smoking habits, age, Body Mass Index (BMI), habitual choices in breastfeeding, and bra-wearing habits were obtained from the patients’ files. Existence of fistula, hyperemia, and breast pain were noted. Data on the existence of abscess, diameter of breast lesions and the existence of multifocality were obtained from radiological examination reports. Pathological specimens were re-evaluated in order to score the severity and extent of inflammation separately for interstitial, perilobular, intraepithelial and luminal compartments. Inflammation was scored visually using a modified version of the histopathological classification system developed by Nickel et al (15).

Lactation period, BMI and number of births were analysed by ROC (Receiver Operating Characterstics) (Med Calc Software, Belgium). Having BMI over 31 BMI (ROC area 0.8±0.04), lactation period over 18 months (ROC area 0.9±0.05), and giving births three or more (ROC area 0.83±0.08) were found to be significant. For this reason, these factors were accepted as risk factors.

Obtained data was evaluated by SPSS 15.00 (SPSS Inc. Chicago, IL, USA). Nonparametric comparisons were performed by chi-square and parametric comparisons were performed by Student’s t-test. p values <0.05 were accepted as significant.

Results

Within the initial group of 110 patients who presented with IGM, we were able to obtain complete clinical, radiological, pathological and follow-up data for 63 patients, who were then included in our study. The mean age of the patients was 38.6±8.4 (23-61). There were 8 recurrences (%12.6) in our study, who underwent subsequent re-excision of affected tissue. None of the patients in our study had Sjögren’s syndrome or hyperprolactinemia. In order to determine the risk factors, we compared the patients with and without recurrences. Contraception usage, parity, age of first birth, affected breast (left or right), bilateral disease, bra-wearing habits or smoking didn’t show any significant difference between two groups (p>0.05). The existence of hyperemia or breast pain was again not significant (p>0.05). The ultrasonographic mean diameters of the breast lesions in two groups or multifocality were also not statistically different (p>0.05). As a pathological risk factor, interstitial, perilobular, or intraepithelial inflammation scores didn’t show a statistically significant difference between patient groups. Histopathological examination revealed features of granulomatous process with multi-nucleated giant cells, epithelioid cells and macrophages forming non-caseating granulomas around lobules; neither evidence of malignancy nor any specific organism was found. Absence of caseous necrosis was marked in the granuloma, which was surrounded by micro abscesses. Most of the cases (22 of the 33 cases) in our study had mixed inflammation and 11 cases had chronic inflammation. Interstitial inflammation was observed in all cases but perilobular, luminal and intraepithelial inflammation were less frequent. Granuloma formation was not observed in 4 cases, but intense mixed inflammation was seen with marked histiocytic infiltration. Abscess formation was observed in %45.4 of cases in our study. (Figure 1-3)

The number of births, duration of lactation, BMI, presence of fistulas, abscess formation detected in ultrasonographic examination and luminal inflammation were found to be significantly different between recurring and non-recurring patients (Table 1). After defining the

Figure 1. Sections of the breast biopsy showed replacement of breast tissue by a diffuse inflammatory infiltrate of histiocytes and lymphocytes with some epithelioid multi-nucleated giant histiocytes (a. hematoxylin and eosin, x100; b. hematoxylin and eosin, x200)
factors which are significantly different between recurrence and non-recurrence cases, we classified risk factors into a) patient related, b) discovered during physical examination, c) radiological and d) pathological. Number of births higher than 2, breastfeeding for more than 18 months, and a BMI higher than 30 were implicated as patient related risk factors for recurrence. The presence of fistulas was regarded as a clinical risk factor whereas abscess formation detected by ultrasonographic examination was accepted as a radiological risk factor. A luminal inflammation score higher than 2 was noted to be a pathological risk factor. The presence of each risk factor then was given a score of 1 and a total risk score was then calculated for each patient (Table 2). The mean idiopathic granulomatous mastitis scores of patients with and without recurrence were 5.1 and 1.9, respectively. The difference was statistically significant (p<0.001) (Table 1).

**Discussion and Conclusion**

Idiopathic granulomatous mastitis is a benign aseptic inflammatory disease of the breast without an obvious etiology. The disease is seen in young- or middle-aged women within a couple years after giving birth. The disease is localized to the breast without any systemic findings (12, 13). Non-puerperal breast secretion has been implicated in the pathogenesis of IGM. An autoimmune reaction against secretions that leak to the interstitium from breast lobules is the suspected mechanism of the disease. This reaction may lead to mass formation, hyper-

**Table 1. Significant differences between recurrent and nonrecurrent cases**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No recurrence</th>
<th>Recurrence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>38.4±8.7</td>
<td>40.1±6.2</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4±4.8</td>
<td>33.8±1.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of Births</td>
<td>2.0±0.8</td>
<td>3.8±1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of lactation</td>
<td>15.6±9.2</td>
<td>33.6±10.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Fistula presence (%)</td>
<td>8 (%14.5)</td>
<td>9 (%16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abscess presence (%)</td>
<td>9 (%16.5)</td>
<td>7 (%12.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Luminal inflammation</td>
<td>2.1±0.9</td>
<td>5.0±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>GM Total</td>
<td>55</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; GM: granulomatous mastitis

**Table 2. Idiopathic Granulomatous Mastitis Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Births, n</td>
<td>&lt;2</td>
<td>3≥</td>
</tr>
<tr>
<td>Duration of Lactation, months</td>
<td>&lt;18 months</td>
<td>18 months ≥</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt;31</td>
<td>31≤</td>
</tr>
<tr>
<td>Luminal inflammation score higher than 2.</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Existence of fistula</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Abscess collection in USG examination</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

BMI: body mass index; USG: ultrasonography
emia, pain, ulceration, abscess, and fistulae. Possible correlation with a number of agents, such as local irritants, viruses, myotic and parasitic infections, tuberculosis, hyperprolactinemia, diabetes mellitus, smoking, and alpha-1 antitrypsin deficiency have been postulated, but have never been clearly demonstrated to be related with the severity or recurrence of the disease. (9-14, 16, 17).

There is no ideal definitive treatment strategy for IGM. Oral contraceptives, surgery, antibiotics and immunosuppressive treatment are the preferred treatments for the IGM (1, 3, 16, 18). The failure of the treatment is the recurrence of IGM and the excision of breast tissue ensures negative margins for IGM with low recurrence rates. However, the surgical treatment has unfavorable cosmetic results. On the other hand, some cases can be easily treated by oral corticosteroids (3). For this reason, several studies prefer step-by-step treatment for the management as starting with antibiotics and then steroids and finally surgery (3, 6, 17). The response to the preferred treatment probably depends on the severity of the IGM. Severity of IGM result in recurrences after preferred treatment. For this reason, several studies have been performed for the risk factors for recurrences (10, 11, 13, 14).

In our study, we evaluated the risk factors for IGM recurrences and selected these factors for defining the severity score for IGM.

Microbiological agents such as Corynebacterium spp. have been implicated in the pathogenesis of IGM. Previous studies have shown that antibiotic treatment can be beneficial in the management of the disease (16, 17). However, we did not consider these factors for severity assessment due to a limited number of studies and insufficient evidence linking specific microbiological agents to IGM (19, 20). On the other hand, contact with wild household mice has been shown to be a risk factor for IGM in the study of Oltean HN et al. (10). This correlation might be related to infectious agents, but Asoglu O et al. (6) in a separate study, was not able to identify any microbiologic agents with sufficient evidence to be causal for IGM. In our study, patients received oral antibiotics in order to suppress possible infectious mastitis, which might complicate underlying IGM and to treat any possible infectious mastitis before the steroid treatment as is recommended in the study of Omranipour R et al. (8).

Oral contraceptive (OCS) use, which is another factor that has been implicated in IGM, has been known to increase breast secretions. However, in our study, no significant association was detected between OCS use and IGM. The association between IGM and OCS use has been reported to range between 0%-42% in a number of previous studies (13). Similarly, the association between IGM and smoking habits is not significant in recent studies, ranging between 0%-50% (10). This wide range, coupled with the limited number of cases in the aforementioned studies, is not sufficient to accept smoking and OCS use as a risk factor.

Parity has also been considered in the aetiology of IGM, in which hormonal changes (hyperprolactinemia) after birth lead to increased breast secretions and subsequent inflammation. After giving birth, breast lobules switch to a secretory phenotype and ductules are found to be dilated. This is hypothesized to be an initiating factor for IGM (1). Similarly, almost all studies on subject to date have reported parity to be associated with IGM (10). As the number of births increase, the incidence of IGM is also increased as reported in a previous study (10).

In our study, all patients had a history of parity and recurrent cases had a high number of births (Table 2). For this reason, we included multiparity as a factor in our risk assessment.

During lactation, breast tissue secretes milk as long as breastfeeding continues. Breast lobules under prolactin stimulation secrete protein-rich liquid, and the ducts remain dilated. It has been reported that prolonged breastfeeding might result in long-term distention of acini and ducts; this may facilitate rupture of these structures, resulting in a granulomatous inflammatory response (21). Several studies have reported an association between breastfeeding and IGM (14, 16, 17). Non-alternating breast feeding was a risk factor for IGM in previous studies (10, 13, 21). Continuing milk secretion without breastfeeding leads to milk stasis and predisposes to mastitis in that breast. However, it is hard to define and measure the breastfeeding habits of each participant, since breastfeeding practices often vary considerably between mothers. In our study, breastfeeding for longer than 18 months was implicated as a risk factor for IGM recurrence.

Body mass index is used as an indicator of obesity in a population. Although BMI has not been previously evaluated in IGM patients, we realized that obese patients with IGM had high recurrence rates. Even though BMI is not an indicator of breast volume or adipose tissue extent, inflammation has been known to spread faster through adipose tissue (22). This might lead to a more complicated IGM presentation in obese patients and render such patients more prone to recurrence.

Patients with IGM generally present with a breast mass that is initially difficult to differentiate from breast cancer. Breast imaging should be performed for differential diagnosis. As most of the patients are younger than 40 years of age, mammaary ultrasound is the preferred method. Inhomogeneous hypoechoogenicity with internal hypoechoic tubular lesions might suggest the possibility of IGM (23). Increased parenchymal echo pattern, with multiple irregular hypoechoic masses with finger-like projections, are the most reported ultrasonographic findings in patients with IGM (23). Abscess formation can also be detected via USG and have been reported at varying rates (6%-43%) (1, 23). Abscess formation is a complication of IGM and might be a factor for severity of IGM. In our study, the ultrasonographic detection of a breast abscess increased the recurrence rate (Table 2).

Inflammation in IGM starts around lobules (24). As the disease progresses, this inflammation reaches duct lumens and the interstitium (25). In our study, it was seen that recurrent cases with dominant fistula formation had prominent luminal inflammation. It might be postulated that severe inflammation, starting from breast acini, can progress into the breast ducts, causing eventual rupture of ducts and acini with a subsequent heavy interstitial inflammatory reaction against milk proteins and cellular fragments, which can then organize into abscesses that fistulize to the skin. As a result, the extent and severity of luminal inflammation are reflected as a higher recurrence rate for the patient.

Granulomatous mastitis is one of the more distressing breast diseases in women. There is no current consensus on the etiology, classification and severity of the disease (26). This is the first study, to our knowledge, to explore the utility of a combined clinical, radiological and pathological risk factor score in determining IGM recurrence risk. One of the main problems facing the clinician in managing IGM patients is the lack of an established disease classification system for IGM, which makes it harder for the clinician to stratify patients according to recurrence risk and make an informed decision on the appropriate treatment modality. This study might help establish a baseline for future studies that aim to establish a definitive classification system for IGM. By using this severity scoring system, the treatment can be designed...
in a precise manner. Low-risk patients can be treated without surgery; on the other hand, high-risk patients might be referred directly to the surgical treatment without wasting time with medical therapy. Steroid treatment in high-risk patients not only results in delay of the treatment but also has risks of steroid complications. This scoring system does not only guide the treatment but may also aid presenting the patient in medical language.

The relatively low number of patients with recurrences is the main limitation of our study, which also rendered our data unsuitable for regression analysis. As the IGM is a rare disease, multi-center studies are needed in order to overcome this limitation. Being a retrospective type is the other limitation for our study. But there is no bias nor irrelevant data in our study. Although this study is retrospective, pathological specimens are re-evaluated for the new scoring system. As being the first, we hope that prospective studies performed in future would overcome these limitations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University.

Informed Consent: Written informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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