Research Article

Combined Treatment Method Comparison Of Medical And Surgical Treatment In Idiopathic Granulomatous Mastitis

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Abstract:
Aim: Our aim in conducting this study was to ascertain the clinical, pathological, and radiological characteristics of patients diagnosed with idiopathic granulomatous mastitis in our clinic and to contribute to related literature by creating a therapy algorithm for granulomatous mastitis.

Method: A total of 62 patients diagnosed with granulomatous mastitis in our clinic were classified into three groups as per the mode of treatment they received. Among these, 20 patients who had only been administered corticosteroids were allocated to Group I, while 18 patients who had received surgical treatment in addition to corticosteroid treatment were allocated to Group II, and 24 patients who had only received surgery were allocated to Group III.

Results: All the cases were female patients. The mean age of the patients was 33.67 ± 6.35 (21-48). No statistically significant difference was found among the groups as per the mean age figures, pregnancy, breastfeeding, oral contraceptive administration, smoking and alcohol use, and family history (p>0.05). 49 (77.4%) patients were diagnosed with granulomatous mastitis by thick-needle biopsy, 7 (11.2%) by incisional biopsy, 4 (6.4%) by excisional biopsy, and 3 (4.8%) by fine-needle aspiration biopsy (FNAB) before the onset of treatment. The median value for the follow-up of the patients was 40 (6-81) months and there was no statistically significant difference among follow-up periods (p: 0.51). 15 (24.1%) patients among all the cases had recurrence. There was a statistically significant difference among the groups with regards to recurrence (p: 0.015).

Conclusion: Granulomatous mastitis may simulate breast cancer both clinically and radiologically. Recurrence is observed in patients who only received corticosteroid or surgical treatment. The combination of corticosteroid and surgical treatment significantly reduces the rate of recurrence. Therefore, this combination can be recommended as selective treatment.

Keywords: Wide local excision, granulomatous mastitis, mammary abscess.

Introduction

Granulomatous mastitis (GM) is an inflammatory, benign, and chronic disease of the breast rarely seen and whose etiology has not been fully sorted out (1, 2). Two types of GM have been defined as idiopathic (granulomatous lobular mastitis) and specific granulomatous mastitis. Tuberculosis, sarcoidosis, and various mycotic and parasitical infections can be listed among the specific etiological causes but the patients are often idiopathic (2, 3).

Many theories have been set forth in order to explain the etiology of the disease (1-4). Studies in literature are not only limited to the issue of etiology but continue to be conducted on the treatment of the granulomatous disease as well. The current modes of treatment include close follow-up, immunosuppressive medication, and surgical excision (3-5). Corticosteroid, colchicine, methotrexate, or azathioprine can be listed among the immunosuppressive medication. If corticosteroid is to be administered, 0.8 mg/kg/day/oral prednisolone is the preferred medication. The duration of treatment is 6 months on average. A 50% rate of recurrence, however, has been reported following the tapering of therapy. There are studies which have argued that surgical excision both enabled definitive diagnosis and was therapeutically superior (4).

The controversy about the treatment of the disease is going on as the modes of treatment have various advantages alongside disadvantages and because of the lack of studies that have shown none of the modes was superior over the other.

The aim of our study, therefore, was to retrospectively compare the modes of treatment, duration of follow-up, and
recurrence in patients with idiopathic granulomatous mastitis treated at our clinic and to shed light on the discussions about the selection of modes of treatment.

Material – Method

The files of a total of 62 patients histopathologically diagnosed with idiopathic granulomatous mastitis at our clinic were retrospectively investigated. All the information on the cases were reviewed and recorded. Four patients who did not show up for follow-ups and the patients who were diagnosed with tuberculosis-related granulomatous mastitis were excluded from the study.

All the patients had USG imaging. Moreover, Magnetic Resonance Imaging (MRI) was performed for 18 patients while mammography (MMG) was performed for 10 patients in addition to USG. Among the imaging techniques, mammography was not performed for patients younger than 35 years of age. All the radiological evaluations were conducted by the same radiologist.

All the patients received one of the biopsy methods such as fine-needle aspiration biopsy (FNAB), thick-needle biopsy, excisional biopsy, or incisional biopsy before the onset of treatment. Surgical samples were initially analyzed macroscopically. Four-millimeter sections were cut from the paraffin-embedded biopsy samples fixed in formaline and they were stained in hematoxylin eosin (HE) to be evaluated by a light microscope. Such fungal stains as the Periodic acid-Schiff (PAS), Ehrlich-Ziehl-Neelsen (EZN), and Gomori Methenamine Silver (GMS) were used in the definitive diagnoses in cases where needed.

The patients were classified into three groups as per the mode of treatment they received:

- **Group I** (n=20): Patients who were only administered corticosteroid. The patient group in which methylprednisolone was started on a 0.5- 0.8 mg/kg/day dose and the dose was tampered according to response to therapy.
- **Group II** (n=18): Patients who received surgery in addition to steroid treatment. The patient group in which methylprednisolone was started to be administered on a 0.5- 0.8 mg/kg/day dose for a week, then the dose was gradually tampered down to 0.1 mg/kg/day within 8 weeks followed by patients’ receiving surgical treatment.
- **Group III** (n=24): Patients who only received surgical treatment. The patient group in which all the inflammatory mass was widely removed so as to achieve negative surgical borders.

Patients’ information was recorded into a database. The patients’ address and telephone information were accessed from their files in order to invite them for follow-ups and their treatment outcomes were recorded. Post-treatment control USG for breast was performed for all the patients. Recovery was set as the elimination of symptoms in the follow-ups, of signs in physical examination, and of the mastitis condition radiologically. The patients included in the study were evaluated with regards to age, symptom, the date when the symptoms started, the breast and quadrant where mastitis is located, pregnancy, breastfeeding, oral contraceptive (OCC) intake, smoking, alcohol abuse, family history, radiological results, mode of treatment, duration of follow-up, and recurrence.

The patient groups with surgical treatment were compared regarding the size (cm), presence of skin excision, and cosmetic outcomes according to the longest diameter of the excised piece.

Statistical Analysis

The data collected within the scope of the study were analyzed by SPSS statistics software (Statistical Package for the Social Sciences 15. 0 for Windows Chicago, IL). The categorical measurements were evaluated in numbers and percentages, while continuous measurements were utilized in mean and standard deviation figures (alongside with median and minimum-maximum figures where necessary). The chi-square test was used in the comparison of categorical variables. The ANOVA test was utilized in the parametric tests among the groups, while the Kruskal-Wallis test was used to compare non-parametric values. Statistical significance level was set at p<0.05.

Results

Clinical evaluation

While all the cases were female patients, their mean age was 33.67 ± 6.35 (21-48). A great majority of the patients were in their 3rd and 4th decades, while only three patients were in their post-menopausal stage. The most common presenting complaint by the patients was a hard, palpable mass. Moreover, the most frequent sign detected during physical examination was hard lesion with irregular borders. Table 1 summarizes the presenting symptoms and physical examination signs of the patients.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Hard mass</td>
<td>42 (67.7 %)</td>
</tr>
<tr>
<td>Ulcerated skin lesion</td>
<td>10 (16.1%)</td>
</tr>
<tr>
<td>Pain and sensitivity</td>
<td>10 (16.1%)</td>
</tr>
<tr>
<td>Hard mass with irregular borders</td>
<td>40 (64.5%)</td>
</tr>
<tr>
<td>Axillary lymph adenopathy</td>
<td>15 (24.2%)</td>
</tr>
<tr>
<td>Nipple retraction</td>
<td>14 (22.5%)</td>
</tr>
<tr>
<td>Abscess</td>
<td>7 (11.2%)</td>
</tr>
<tr>
<td>Sinus formation</td>
<td>6 (9.6%)</td>
</tr>
</tbody>
</table>

Two of the patients did not have a history of pregnancy, while five did not have a history of breastfeeding. 14 (22.5%) of the patients were on OCC, while 11 (11.2%) were smokers. None
The disease was detected in the left breast in 32 (51.6%) patients, while it was seen in the right breast in 30 (48.4%) patients. It was seen to be located in the lower-external quadrant of the breast in 18 (29%) patients, in the upper-internal part in 16 (25.8%), in the upper-external part in 14 (22.5%), and in the lower-internal quadrant in 14 (22.5) patients.

**Radiological Evaluation**

The most common signs that the results of the USG revealed were skin thickening, parenchymal edema, asymmetrically distributed coarse heterogeneous parenchyma, and areas lacking clear borders with sporadic fluid density. According to USG results, 8 (12.9%) of patients were suspected to have malignancy as per the BI-RADS classification.

The most frequently observed signs as revealed by the results of the MRG included skin thickening, parenchymal edema, and asymmetric parenchymal staining. According to MRG results 7 (38.5%) patients were suspected to have malignancy. Furthermore, the most commonly seen sign in MMG was the increase in asymmetric density. Table 3 presents the radiological features of the patients.

### Table 3. Ultrasonography, magnetic resonance imaging and mammographic features in patients with idiopathic granulomatous mastitis

<table>
<thead>
<tr>
<th>Imaging Method</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Ultrasoundography (n= 62)</strong></td>
<td></td>
</tr>
<tr>
<td>Skin thickening and parenycmal edema</td>
<td>30 (48.3 %)</td>
</tr>
<tr>
<td>Asymmetrically distributed coarse</td>
<td>21 (33.8 %)</td>
</tr>
<tr>
<td>Enlarged axillary lymph nodes</td>
<td>20 (32.2 %)</td>
</tr>
<tr>
<td>Enlarged ductus</td>
<td>15 (24.1 %)</td>
</tr>
<tr>
<td>Thick capsulated cyst with high inner density</td>
<td>6 (9.6 %)</td>
</tr>
<tr>
<td>Abscess fistulated to the skin</td>
<td>5 (8 %)</td>
</tr>
<tr>
<td>BI-RADS 4 and higher</td>
<td>8 (12.9 %)</td>
</tr>
<tr>
<td><strong>Magnetic Resonance Imaging (n= 18)</strong></td>
<td></td>
</tr>
<tr>
<td>Skin thickening and parenycmal edema</td>
<td>14 (77.7 %)</td>
</tr>
<tr>
<td>Asymmetrical parenchymal staining</td>
<td>10 (55 %)</td>
</tr>
<tr>
<td>Enlarged axillary lymph nodes</td>
<td>9 (50 %)</td>
</tr>
<tr>
<td>Nipple retraction</td>
<td>8 (44.5 %)</td>
</tr>
</tbody>
</table>
Enlarged ductus with peripheral staining & 4 (22.2 %) \\
Parenchymal distortion & 2 (11 %) \\
Nodular lesion with heterogeneous outlook & 2 (11 %) \\
BI-RADS 4 and higher & 7 (% 38.5) \\
Mammography (n= 10) & \\
Asymmetrical density increase & 8 (80 %) \\
Hypoechoic mass with heterogeneous irregular borders & 1 (10 %) \\
Nipple retraction & 1 (10 %) \\
Normal & 1 (10 %) 

Pathological evaluation

48 (77.4%) patients were diagnosed with granulomatous mastitis before the treatment through thick-needle, 4 (6.4%) through excisional biopsy, 3 (4.8%) through FNAB. 7 (11.2%) patients with mammary abscess were diagnosed through incisional biopsy carried out during abscess drainage.

The results of histopathological evaluation revealed that all cases had non-caseating granuloma structures upsetting the lobular structure. These granulomas were composed of a great number of multi-nuclear giant cells, lymphocytes, plasma cells, epithelioid histocytes, and some neutrophils and eosinophils. No microorganisms could be detected through EZN, GMS, or PAS staining.

The mean size of the excised piece as per its longest diameter was measured to be 5.05±1.16 cm in Group II, while it was 7.16±1.68 cm in Group III in macroscopic analyses (p>0.05). When presence of skin excision was investigated in the removed tissues, it was observed in 5 patients in Group II while 10 patients in Group III had it (p>0.05). When both the mean piece size and the presence of skin excision were investigated, it was seen that the rates in Group III were high but the result was not statistically significant (p>0.05).

Follow-up

The median duration of follow-up for all patients was 40 (6-81) months. No statistically significant difference was observed among the groups with regards to the duration of follow-ups (p: 0.51). 15 (24.1%) patients had recurrence. 6 recurrent cases were present in Group I and 9 recurrences were seen in Group III, while there was no recurrence in Group II. There was a statistically significant difference among the groups as revealed by the comparison of recurrence rates (p: 0.015).

All the patients in Group I with recurrence received the wide local excision procedure. No recurrences were observed in the follow-ups of these patients. 6 patients out of 9 with recurrence in Group III received wide local excision once again, while 3 received the wide local excision procedure in addition to corticosteroid treatment. 2 patients out of 6 who received wide local excision were observed to have recurrence.

There was no significant difference between Group II and Group III regarding cosmetic satisfaction. 2 patients were detected to have granulomatous mastitis in the opposing breast as well during the follow-ups. Table 4 presents the duration of follow-ups, presence of recurrence, and postoperative cosmetic satisfaction according to the groups.

Table 4. Duration of follow-up, presence of recurrence, and postoperative cosmetic satisfaction of the patients according to the groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up value (minimum- maximum)</td>
<td>40 (6-78)</td>
<td>36.5 (6-81)</td>
<td>38.5 (6-78)</td>
<td>0.51</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Yes</td>
<td>6 (% 30)</td>
<td>0</td>
<td>9 (% 37.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>14 (% 70)</td>
<td>18 (% 100)</td>
<td>15 (% 62.5)</td>
</tr>
<tr>
<td>Cosmetic satisfaction</td>
<td>Good</td>
<td>-</td>
<td>16 (% 88.8)</td>
<td>20 (% 83.3)</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>-</td>
<td>2 (% 11.2)</td>
<td>4 (% 16.7)</td>
</tr>
</tbody>
</table>

(* Differences between the groups with Chi-square test is statistically significant p<0.05)

Discussion

Granulomatous mastitis is a rare inflammatory disease of the breast whose etiology is not fully known. It was first defined by Kesler and Wolloch in 1972 (6).

Idiopathic granulomatous mastitis is generally seen in the young middle ages (3rd-4th decades) and in the 1st-2nd postpartum year (7). Virtually all the series include young women but it can also be seen in all age groups. There are cases of male patients reported in literature as well (3, 8, 9).
Most of our patients were in their pre-menopausal period with majority of them in the 3rd–4th decades. While all our patients were female, their mean age was found to be 33.67 ± 6.35 (21-48).

Many pathological processes can be held accountable for the granulomatous inflammation of the breast (6, 10). Some authors have suggested that the cause for the disease could be an autoimmune process, indeterminable microorganisms, or a response to labor (11). The results of serological tests for ANA and RF antibodies which serve as proofs to autoimmunity, however, are generally found to be negative (12, 13). Moreover, there are also studies that have shown that the disease was correlated to OCC administration and breastfeeding (6, 8, 14, 15). It was associated with smoking as well but the association could not be fully explained in some studies (12). Most of our patients had a history of pregnancy and breastfeeding in line with literature but the rates of OCC, smoking, and alcohol use were at a low level.

The most common presenting complaint is the palpable mass in the breast. It may manifest as swelling or abscess. It may cover the skin over the swelling or manifest itself with nipple retraction, sinus formation, or axillary lymphadenopathy by penetrating into the pectoral muscle under the swelling (15-16). It is equally seen in both breasts and the lesion may be located in any quadrant of the breast (17). The most common complaint among our patients was a hard palpable mass and the disease was unilateral in all the cases. During the follow-ups two patients were detected to have granulomatous mastitis formation in the opposing breast as well. Seven patients had abscess. The disease was observed in the left breast in 32 (51.6%) cases, while it was in the right breast in 30 (48.4%) patients. The disease was seen to be present in all the quadrants of both breasts.

The USG image of granulomatous mastitis is not specific and it is often seen as a heterogeneous hypoechoic mass with irregular borders and hypoechoic tubular extensions persistent with the mass (18-19). MMG is most commonly seen as focal asymmetric opacity (18). Some studies have utilized MRG and indicated focally homogenous growing masses with irregular borders (20, 21). Doppler has been used as well and shown increased vascularization within or around the lesion (22). The results of USG in our study most frequently showed skin thickening, parenchymal edema, asymmetrically distributed coarse heterogeneous parenchyma, and areas without any clear borders sporadically containing fluid density. MRG, on the other hand, indicated skin thickening, parenchymal edema, and asymmetric staining. Moreover, the results of MMG most commonly showed asymmetric density increase.

Histopathological analysis shows non-caseating granuloma structures upsetting the lobular structure. A great number of multi-nuclear giant cells, lymphocytes, plasma cells, epithelioid histocytes, neutrophils, and eosinophils can be seen. Micro-abscess foci can be observed as well (23).

The optimal treatment for granulomatous mastitis remains to be clarified. The current modes of treatment include close follow-up, immunosuppressive medication, and surgical excision (3, 5, 12). GM is generally sterile; therefore, there is no need to introduce antibiotics treatment. Most of the authors have reported negative bacterial culture in their series (3). GM, however, can sometimes be complicated with abscess formation with mixed aerobic and anaerobic infection and chronic suppuration. Antibiotics should be administered after such conditions (16). Seven patients had abscess in our study. No reproductions were detected in their abscess cultures obtained during drainage. Empirical antibiotics treatment was initiated for these patients pending their culture results.

Corticosteroid administration in the treatment of granulomatous mastitis is first suggested by Dehetrogh et al. (24). Moreover, there are also studies which have shown that corticosteroid treatment was useful in some resistant cases where no organisms could be found (25). Corticosteroids should be started at a daily dose of 1mg/kg/day and should slowly be tampered according to clinical response (17). Corticosteroid treatment might be continued at a high dose until the lesions are completely eliminated. Response to treatment is seen within the first week but sometimes complete recovery may take a couple of months (3, 17). It has also been mentioned that recurrence was seen following the stopping or lowering of dosage of corticosteroid treatment in more than half of the recurring cases (17, 20). Patients on corticosteroid treatment should be closely followed up with regards to glucose intolerance and Cushing’s disease (12). The elimination of tuberculosis particularly in underdeveloped countries proves to be important before initiating corticosteroid treatment. Successful treatment has also been reported by methotrexate and azathioprine administration. In this manner, immunosuppressive treatment was found to reduce corticosteroid use, control the inflammatory process, and prevent following complications (5, 25). The recommended treatment of IGM is complete surgical excision in combination with corticosteroid administration as the disease in autoimmune-based (12, 26, 27).

Granulomatous mastitis may simulate breast cancer both clinically and radiologically. Recurrence is seen in cases where solely corticosteroid or surgical treatment is performed. The combination of corticosteroid administration and surgical treatment significantly reduces the rate of recurrence. Therefore, this combination can be recommended as selective treatment.


