ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is a benign inflammatory breast disease of unknown etiology that affects women in their reproductive period. The most commonly preferred option as first-line treatment is steroids, but the lack of a standard treatment protocol and high recurrence rate after treatment constitutes a recurring challenge during its management. The aim of this study was to investigate whether the decision to end the treatment should be made radiologically or clinically.

Materials and Methods: This retrospective cohort study included IGM patients who had complete clinical recovery with steroids and were followed for a minimum of 30 months. Patient demographics, disease severity and findings, treatment regimens and duration, and magnetic resonance imaging (MRI) findings at clinical recovery were assessed for their relation to recurrence.

Results: Eighty-nine patients who were clinically completely healed after steroid treatment for IGM were included in the study. At the time of clinical healing, 51 (57.3%) patients had a complete radiological response and 38 (42.7%) had a partial radiological response (PRR) on MRI. Overall, recurrence developed in 22 (24.7%) patients after a median 38.6-month follow-up. Patients who experienced recurrence were significantly older and had PRR when their treatment was stopped upon clinical healing.

Conclusion: During the process of clinical healing, the imaging findings revealed that the remaining disease seems to be a significant predictor for recurrence in IGM patients. In patients with PRR, extending the treatment with either prolonged steroid therapy or by surgical excision of the occult residual disease may prevent recurrences in IGM patients.

Keywords: Granulomatous mastitis; steroid treatment; recurrence; MRI

Introduction

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory breast disease of unknown etiology that affects women of reproductive age (1). The lack of a standard protocol for its treatment, high anxiety among patients due to its mimicking of malignancy with clinical and radiological findings, and the high recurrence rate after treatment are the challenges of managing this disease. Although it has endemic proclivity in Middle Eastern and Asian countries mainly, these challenges also constitute a problem for Western clinicians due to immigration. In general, diagnosis is not difficult for physicians in
endemic areas. Although physicians can diagnose IGM easily, they deal with challenges when managing the disease owing to its presentation as well as after recurrence.

Surgery was the primary treatment for many years, even after the effectiveness of steroids was reported and proven in 1980 (2). However, the clinical efficacy of steroids as a first-line treatment, rising to 90%, was somewhat undermined by recurrence rates of up to 46% following treatment discontinuation (3). In addition, the side effects of steroids during the long-term treatment reduce compliance with the treatment for the patients (4). Given these factors, surgery has again become the preferred first-line treatment (5-7). However, reported recurrence rates of surgical excisions are similar to those found after steroid therapy, therefore limiting its feasibility (8,9). Moreover, either repetitive interventions or wide surgical excisions may be required to achieve remission, which leads to poor cosmetic results. The complexity of the management of IGM has prompted investigation of the factors associated with disease recurrence.

Although there have been many studies considering the dosage, time, and methods used to apply steroids, to date there had not been a study regarding the optimal end-point to discontinue treatment. Complete clinical response (CCR) was the criterion to discontinue the treatment in the search for the effectiveness of steroid treatment, in accordance with the studies to date (10). However, there is no standardized and objective definition of CCR. In addition, it has been shown that there are residual findings of disease that are only evident on imaging which were present in up to 50% of the patients with CCR (4).

Imaging modalities such as ultrasound (US) and contrast-enhanced magnetic resonance imaging (MRI) are used routinely in the diagnosis of IGM (11, 12). US possesses the distinct advantages of high sensitivity, non-invasiveness, and is valuable in screening patients in cases of mild disease. In contrast, MRI is a useful imaging modality for the differential diagnosis of breast cancer and it may also be more useful for indicating active lesions and locate the extent of the lesions (13). Therefore, MRI has been used in the evaluation of the response to steroid treatment (4, 13).

The aim of this study was to investigate if the decision to end treatment should be made radiologically or clinically and to assess the factors which may have an impact on recurrence after steroid treatment in a cohort of IGM patients who had undergone steroid treatment and also had long-term follow-up.

Materials and Methods

Study Design

The study was planned as a retrospective cohort design and conducted at a tertiary breast care unit. The study protocol was approved by the institutional ethics committee. Patients with a diagnosis of IGM who were treated with steroids as first-line treatment and had achieved CCR were included in the study. IGM patients who did not receive their steroid treatment according to the planned regimen or did not have a satisfactory response to the treatment or had a follow-up of less than 30 months after clinical recovery or did not have an MRI exam at the time of clinical recovery were excluded from the study (Figure 1). The minimum follow-up period of 30 months was chosen as this was the time of latest recurrence of IGM in our records after full clinical recovery among all IGM patients who only received steroid therapy.

Study Groups

Following CCR, the reappearance of clinical symptoms and/or findings, such as palpable mass, erythema, fistula-formation, skin ulceration, and abscess formation suggesting IGM in the same breast was regarded as recurrence.

The patients were grouped according to their radiological findings at the termination of steroid therapy when patients became symptom-free. The patients who had the findings suggesting residual IGM disease on MRI (abscess formation, heterogeneous mass, skin thickening, unresolved fistula tracks, contrast-enhanced appearances) were designated Group partially radiological response (PRR), whereas those with no such radiological findings were designated Group complete radiological response (CRR).

Study Outcomes

The primary aim was to assess the impact of MRI findings at the time of CCR on predicting the recurrence in IGM patients who only received steroids as their treatment. Therefore, the rate of recurrence in both study groups was compared. As a secondary outcome, demographic and clinical variables related to IGM which may have an independent impact on the recurrence were also analyzed.

Variables

Patients’ features and demographics, clinical findings and extension of the disease, treatment history including the type of agents and their duration, and MRI findings at the end of the treatment were collected from patient files for univariate and multivariate analysis.

Steroid Treatment Protocol

Patients in the study cohort received three different regimens of steroids. Some patients received only topical, some others received only IGM: Idiopathic granulomatous mastitis
oral steroids and the rest received both. The choice of the treatment regimen was at the physician’s discretion.

Topical steroid administration: Prednasinolone 0.125% pomade (Prednol pomad; Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey) was applied topically by the patients to the affected breast, twice a day on weekdays with breaks during weekends (1-week cycle).

Treatment with oral steroid: Postprandial 0.8 mg/kg oral methylprednisolone (Prednol tablet, Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey) was given once daily.

Combined steroid therapy: Postprandial 0.4 mg/kg oral methylprednisolone was given once daily and Prednasinolone 0.125% pomade – with the same pharmaceutical agent - was applied topically to the diseased breast as described in the topical steroid administration protocol.

Steroid treatment according to the unit protocol was continued until the first signs of disease amelioration were observed. Then the treatment was tapered in patients who received oral methylprednisolone. Topical treatment cycles were ended when CCR was obtained.

Decision for Completion of Steroid Treatment
Following tissue diagnosis and before starting steroid treatment, all patients underwent MRI in order to assess the extent of the disease within the breast. Thereafter, the response to treatment was assessed by physical examination and breast US.

The decision to stop steroid treatment was given according to the clinical responses. The lack of palpable mass and erythema on physical examination, and healing of the skin with the closure of ulceration, and fistula were considered CCR. Patients were also assessed by breast MRI at the end of steroid treatment when CCR was achieved. The lack of image findings indicative of persistent IGM on MRI was regarded as CRR. Any remaining image findings suggesting IGM, such as heterogeneous mass, skin thickening, unresolved fistula tracks, and contrast-enhanced appearances were regarded as PRR (Figure 2).

Follow-up
During the course of treatment, patients were examined for findings suggestive of IGM. After termination of treatment, patients were followed on the first, third, and sixth months, and every six months thereafter. At each visit, a physical examination and breast US were performed to assess the patient for recurrence.

Statistical Analysis
Data were analyzed with Statistical Package for Social Sciences software (SPSS) version 24.0 (IBM Inc, Armonk, NY, USA). Pearson’s chi-square test and Fisher’s exact test were used to compare qualitative data. Normality for the distribution of quantitative variables was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student’s t-test was used to compare normally distributed data. Mann-Whitney U test was used to compare the variables without normal distribution. Multivariate logistic regression analysis was performed to assess variables that may be associated with recurrence. Based on the result of the analysis, a p<0.05 was considered to be statistically significant.

Results

Study Cohort
The study included 222 patients who were diagnosed with IGM between September 2014 and October 2019 at the Breast Unit in Kartal Dr. Lütfi Kirdar Training and Research Hospital.

Among these, surgical treatment was performed as first-line treatment in 24 patients, and the remaining 198 patients received steroid therapy. Of these 198, 89 (44.9%) patients who fulfilled the inclusion criteria remained in the cohort for the current study (Figure 1). Some of the patients in the current cohort were also included in our previous trials with different outcomes and the results were published elsewhere (4, 14).

The mean age of the cohort was 33.2±6.4 years, and 87 (97.8%) patients were of reproductive age. The most common finding was palpable mass (n=85, 95.5%), followed by erythematous appearance (n=72, 80.9%).

MRI Findings at Clinical Recovery

When CCR was achieved and steroid treatment was stopped, 51 (57.3%) had CRR and 38 (42.7%) had PRR on MRI.

Recurrence Rate and Associated Factors

Recurrence was observed in 22 (24.7%) patients after a mean follow-up of 42±10.3 months. Patients who had recurrence were significantly older than those who did not (35.8±6.8 vs. 32.4±6, p = 0.03). Most recurrences were seen in the Group PRR group, as follows: PRR n = 19 (86.4%) vs. CRR group n = 3 (13.6%) and this difference was significant (p<0.001) (Table1).

Multivariate analysis revealed that each one-year increase in age significantly increased the probability of recurrence by around 1.1 times [odds ratio (OR) (95% confidence interval (CI) 1.11 (1.01,
Furthermore, PRR at the end of treatment increased the probability of recurrence by more than 18 times [OR (95% CI) 18.25 (4.48, 74.34), p < 0.001] (Table 2).

For the whole cohort, recurrences were observed at a median of 3.5 months after stopping treatment. Recurrences developed significantly earlier in those patients who had PRR [median 3 months (range: 1–30)] than in those who had CRR [median: 15 months (range: 15–20), p = 0.03].

Discussion and Conclusion

A 24.7% recurrence rate was observed in our IGM cohort, which comprised patients with long-term follow-up, in whom steroids were used as first-line treatment, and treatment was discontinued based on clinical responses. Radiological residual disease at the time of treatment was associated with a higher risk of recurrence. The multivariate analysis confirmed that age and radiological response were the most significant predictors of recurrence.
discontinuation and age was an independent risk factor for recurrence in univariate analysis and persisted on multivariate analysis. Each one-year increase in age significantly increased the probability of recurrence by around 1.1, and PRR at the end of treatment increased the probability of recurrence by more than 18 times. Notably, we found that recurrences developed significantly earlier in those patients who had PRR than in those who had CRR.

To the best of our knowledge, the decision to discontinue medical treatment has been made clinically in all studies to date (10). However, there was no standard definition of complete remission in the treatment of IGM. Complete remission was defined as the absence of pain, swelling, erythema, tenderness, and lump after treatment (15-17), but the radiological responses were never addressed in the decision to cease the treatment. This is the first study investigating the relationship between the radiological responses and recurrences while the decision of treatment discontinuation was made. The long-term follow-up of our series is longer than the ones in the literature and thus has strengthened the results of our study.

Retrospective design and use of different treatment modalities with different time periods—even though all cases were treated with steroids successfully—were the most important limitations of our study. Moreover, recurrence was not found to be related to different treatment modalities and different periods in our series. Another limitation of our study was the use of MRI instead of US, which is more sophisticated and expensive in comparison to the US. MRI is useful for evaluating possible residual disease after treatment or for monitoring the disease in patients who underwent conservative treatment (18, 19).

In our study, the overall recurrence rate with steroid treatment was 24.7%, consistent with the literature. More specifically, it was 5.9% (3/51) in the CRR group and 50% (19/38) in the PRR group. Wang et al. (6) reported a lower recurrence rate in the group with surgical excision following systemic steroid treatment than the group with only systemic steroid treatment (5.1% vs. 22.7%). The high total recurrence rate could be explained by long follow-up intervals and different treatment protocols in our cohort. The patients who received wide surgical excision following systemic steroids in the study of Wang et al. (6) showed similar characteristics to the CRR group in our series in terms of the recurrence rate. Gurleyik et al. (20) reported a similar recurrence rate of 5.3% in 19 patients with local excision following 8 weeks of oral methylprednisolone treatment, in a retrospective cohort. Additionally, Lei et al. (10) reported that management with surgery following treatment with steroids resulted in the lowest recurrence rate (4%) in a meta-analysis. Recurrence rates were low and similar in regard of the patients with CRR in our series. In our opinion, the similarity of the lower recurrence rate is related to the removal of residual disease following steroid treatment.

To the best of our knowledge, there are two studies in the literature investigating the relationship between age and recurrence in IGM (21, 22). Although Yilmaz et al. (22) reported a higher mean age of patients with recurrence (40.1 vs. 38.4 years), there was no correlation between age and recurrence in both studies. Contrary to these studies, we found a statistically significant relationship between age and recurrence.

In recent years, the factors affecting recurrence following the treatment of IGM have been examined in retrospective studies (21-23). Demographics, the number of births, breastfeeding period, smoking, use of oral contraceptives, and the type of pharmaceutical course on the breast were evaluated, and different findings for recurrence were reported in these studies. Uysal et al. (21) found that pregnancy, breastfeeding, previous mastitis, and smoking were related to recurrence in a multicenter retrospective study. In addition, Yilmaz et al. (22) found high BMI, the number of births, breastfeeding period, luminal inflammation, fistula, and abscess to be closely related to recurrence, but smoking was not with a lower recurrence rate (8/63, 12.7%). Even though the treatment modalities were different, all patients received steroids in our study. The number of births, breastfeeding period, smoking, and oral contraceptives were not found to be related to recurrence in our study. Tan et al. (24) reported a recurrence rate of 17.7%. Moreover, different treatment modalities, including antibiotics, steroids, and surgery, were used in their study. Even though it was not significant, inflammatory findings and symptoms in the breast, and previous treatment with antibiotics, were reported to be more common in recurrent cases. Findings in the breast and previous treatment with antibiotics were not related to recurrence in our series.

Altunkeser et al. (25) conducted a retrospective evaluation of MRI findings to predict treatment success in IGM. While they did not find a significant relationship between MRI findings and treatment success, they observed that patients with involvement in the retroareolar region had lower treatment success rates. In our study, we found no significant relationship between the involvement of more than one quadrant in the breast, retroareolar involvement, and recurrence.

We suggest evaluating radiological responses in addition to clinical response when deciding if to discontinue treatment of patients with IGM receiving steroids as first-line treatment. Prolonging the steroid therapy until the achievement of CRR for the disease, or excision with care taken for breast preservation to preserve for radiologically detected residual disease could lower recurrence rates in IGM. Excision of radiologically marked disease may be a reasonable approach. Additionally, studies should be conducted to assess residual disease in patients with CCR using US, a more cost-effective imaging method compared to MRI.

Ethics Committee Approval: The study protocol was approved by Kartal Dr. Lütfi Kirdar Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020/514/177/43, date: 13.05.2020).

Informed Consent: Informed consent was taken from patients to collect and use data.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Conflict of Interest: The authors have no conflicts of interest to declare.

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