

Local Steroid Treatment: An Effective Procedure for Idiopathic Granulomatous Mastitis, Including Complicated Cases

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Abstract

Purpose To evaluate the effectiveness of treatment with topical and intralesional steroids for idiopathic granulomatous mastitis (IGM) and to compare with surgical methods.

Methods Data was retrospectively collected from records. Intralesional steroid injection and topical steroid administration, hereafter referred to as local steroid treatment (LST) were applied in Group 1. Surgery (local excision, wide excision and mastectomy) was performed in Group 2. In Group 1 changes in lesion sizes were recorded and factors complicating treatment were identified. The Numeric Pain Rating Scale was used to determine subjective pain. LST and surgery were compared with regard to: pain before and after the treatment; complication rate; recurrence rate; and treatment cost.

Results There were 38 and 48 patients in Group 1 and Group 2, respectively. In the LST group 72 lesions were present and 70 of 72 (97%) responded completely to treatment. Pre-treatment median maximum diameter was 23.50 (15.25-35.25) mm, which regressed to 16 (12-25) mm after the first session. While the pre-treatment pain scores of Group 1 and Group 2 were similar ($p=0.756$), there was a significant difference in the post-treatment pain scores ($p<0.001$). No recurrence occurred in any patients in Group 1, while recurrence developed in 15 (31.2%) patients in Group 2 ($p<0.001$).

Conclusion LST is a treatment for IGM that is cheap, with high efficiency, negligible recurrence, and has good esthetic outcome. Our results suggest that LST should be the first-line treatment option for all IGM patients, including complicated cases.

Introduction

Idiopathic granulomatous mastitis (IGM) is a benign and chronic inflammatory disease of the breast. It typically affects women of reproductive ages with a recent history of pregnancy and breastfeeding [1]. Although rare, it is also seen in nulliparous women and men [2, 3]. Unlike other inflammatory diseases of the breast, it mimics breast cancer clinically and radiologically [1, 2, 4]. Although many factors associated with increased risk of IGM have been identified, its etiology is still unclear. Breastfeeding, smoking, oral contraceptive pills, hyperprolactinemia, autoimmunity, undetectable microorganisms, some *Corynebacterium* species and diabetes mellitus are some of the suspected predisposing factors in the etiology [1, 5].

Patients usually present with complaints of breast mass and pain. Other typical findings may be skin hyperemia, abscess, fistula, nipple retraction and discharge [6]. When clinical symptoms are suspicious, the patient is first evaluated with imaging methods, such as ultrasonography (USG), X-ray mammography or magnetic resonance imaging. Since the suspicion of malignancy is not allayed in most patients following clinical and radiological evaluations, histopathological examination plays an important role in the diagnosis. For histopathological examination, core needle biopsy, which has a high diagnostic accuracy, is an appropriate sampling method [7].

Optimal treatment and management in IGM is unclear. Options include antibiotherapy, systemic steroid treatment and surgery although some studies have reported spontaneous regression with observation [8, 9]. Although many treatment methods have been tried thus far, there is no consensus on the optimal therapeutic strategy in the literature. The use of medical treatment is increasing due to the cosmetic problems caused by surgical treatments. One medical treatment option includes systemic steroid therapy, which has high effectiveness, but its use is limited due to the wide range of side effects [10]. Use of local steroids is becoming widespread to avoid these systemic side effects.

The aim was to evaluate the effectiveness of the use of local steroids, limited to intralesional injection and topical application, in IGM treatment and to compare with surgical methods in terms of clinical outcomes and patient perception.

Materials And Methods

Patient selection

All female patients over 18 years of age, with a histopathological diagnosis of IGM, presenting between January 2017 and December 2019 at Kocaeli University Research and Application Hospital were included in the study. Data was retrospectively collected from hospital electronic records and patient follow-up forms. Anamnesis, treatment method, histopathological evaluation, imaging and laboratory results, pain score results and all relevant information collected during follow-up were recorded. All tissue and abscess drainage samples from participants were sterile on microbial cultures. Patients were divided into two groups depending on treatment method; the local steroid treatment (LST) group who were treated with intralesional and topical steroid applications and the surgically treated group. Exclusion criteria included: patients who were pregnant or breastfeeding during treatment; had contraindications to steroid use; were treated with methods other than LST or surgical treatment; whose follow-up period was less than 12 months; and patients whose medical records were incomplete.

Treatment Protocols And Endpoints

The patients were divided into two groups, the LST group (Group 1) and the surgery group (Group 2). Intralesional steroid injection was performed in all patients in the LST group prior to topical steroid administration. The injection was performed once a month using 40–80 mg triamcinolone acetonide. Depending on the number and size of the lesions, the active ingredient was diluted with saline solution in the ratio of 1/2 to 1/4 and 1 cc of 2% lidocaine was added. Dosage calculation was made based on the largest dimension of the lesion and steroids in the range of 10–15 mg per 1 cm of diameter were injected into the lesion, under USG guidance. Any abscess present was drained and the steroid was injected into the abscess pouch and surrounding inflammatory tissues. In the presence of fistula, the injection was also applied around the fistula tract. After the intervention, topical triamcinolone acetonide was administered once a day for a month. Clinical and radiological findings of the patients were evaluated

one month after the injection. Treatment responses were evaluated both on the effect on the lesions and the reports of the patients. Following the treatment, complete regression of the lesion as assessed by USG was defined as 'complete response'. If the lesion size remained the same after two consecutive sessions, despite regression in lesion size in earlier sessions, it was defined as 'partial response'. Patients in whom all lesions completely responded to treatment and whose complaints disappeared were accepted as 'complete recovery'. 'Partial recovery' was recorded if the patient's complaint persisted or a partial response was noted in one of their lesions. This procedure was repeated monthly until the treatment result of the patient was accepted as complete recovery or partial recovery. Surgical treatments consisted of local excision, wide excision and mastectomy, as appropriate to the lesion and at the discretion of the surgeon. Surgical treatment was considered to be complete on the day of discharge. Patients whose treatments were completed in both the LST and surgery groups were followed up at one, six and twelve months and then annually thereafter.

Evaluation And Analysis

The change in the size of the lesions was analyzed in relation to the largest dimension of the lesion. After each session, changes in lesion size were calculated at presentation for any subsequent treatment or at first follow-up as absolute measurement and percentage. To identify the factors complicating the treatment, the number of sessions (NoS) needed for complete response was assessed according to the size of the lesion. In addition, NoS needed for complete recovery was evaluated according to the number of lesions in the breast, and presence of fistula and abscess. To examine the relationship between the size of the lesion and NoS for complete response, patients were stratified into two groups, those with a largest lesion dimension < 3 cm or ≥ 3 cm. Lesions with partial response and patients with partial recovery were excluded from this assessment.

Surgical treatment and LST were compared with regard to pain before and after the treatment, complication rate, recurrence rate and treatment cost. The Numeric Pain Rating Scale (NPRS) was used to determine changes in the patients' perception of pain during the treatment process. Patients were asked to score the severity of their pain from "0" (no pain) to "10" (the most severe pain ever experienced). For the evaluation of pain, scores from 1 to 3 were accepted as mild, 4 to 6 as moderate, and 7 to 10 as severe pain. For Group 1, three pain scores were defined: pre-treatment, after the first session and post-treatment. Changes between these scores were examined. For pain after the first session, the scores made one month after the first injection were taken into account. As for post-treatment pain, the scores made one month after the treatment was completed were considered. For Group 2, pre- and post-treatment pain scores were defined. The scores made one month after the operation was used for post-treatment pain. The results of these scores were compared with the results of Group 1. While calculating recurrence rates, the 12-month follow-up period was taken into consideration. The costs of the treatment and follow-up processes of the patients to the reimbursement institution were obtained in Turkish Lira from hospital records. The costs were calculated in US Dollars (USD) at the exchange rate of prevailing invoice date.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Shapiro Wilk tests were used to test the normality of data distribution. Continuous variables were expressed as median and interquartile range (IQR; 25th-75th percentile), and categorical variables were expressed as counts (percentages). Differences between the groups were analyzed by Mann Whitney U test, Kruskal Wallis, One way analysis of variance (ANOVA) and Dunn's Post Hoc test while categorical data was analysed using Yates chi-square test or Monte Carlo chi-square test, as appropriate. Comparisons of non-normally distributed continuous variables between the times were performed using the Wilcoxon t test and Friedman Analysis of variance by Ranks and Tukey Post Hoc Test. Statistical significance was assumed when $p < 0.05$.

Results

Among 108 patients diagnosed with IGM in our clinic, 42 underwent LST, 54 underwent surgery, and 12 were treated with other methods. The records of four patients undergoing LST or surgery were missing, and the follow-up period was less than 12 months for six patients. Consequently, 38 patients undergoing LST (Group 1) and 48 patients undergoing surgery (Group 2) were included in the study. The clinical and etiological characteristics of the patients are shown in Table 1. The mean age was similar in both groups ($p = 0.848$). The number of patients in whom one breast (passive breast) was suckled significantly less than the other was 17 (44.7%) in Group 1, and 22 (45.8%) in Group 2. It was found that IGM developed in the passive breast in 16 (94.1%) of 17 patients in Group 1, and in 20 (90.9%) of 22 patients in Group 2.

Table 1
Clinical characteristics of patients

	Group 1 (n = 38)	Group 2 (n = 48)
Age, mean(SD)	37.2 ± 8.6	36.8 ± 8.6
Parity		
Nulliparous	2 (5.3)	2 (4.2)
Parous	36 (94.7)	46 (95.8)
Oral contraceptive		
Ever used	9 (23.7)	10 (20.8)
Never used	29 (76.3)	38 (79.2)
Smoking		
Yes	9 (23.7)	7 (14.6)
No	29 (76.3)	41 (85.4)
Hyperprolactinemia		
Present	0 (0)	1 (2.1)
Absent	38 (100)	47 (97.9)
Autoimmune disease(s)		
≥ 1	0 (0)	2 (4.2)
None	38 (100)	46 (95.8)
Comorbid disease(s)		
≥ 1	8 (21.1)	8 (16.7)
None	30 (78.9)	40 (83.3)
Localization		
Unilateral	38 (100)	43 (79.6)
Bilateral	0 (0)	5 (20.4)
Passive breast history		
Yes	17 (44.7)	22 (45.8)
No	21 (55.3)	26 (54.2)
Data are given as mean ± SD or n (%).		

	Group 1 (n = 38)	Group 2 (n = 48)
Fistula formation(s)		
Present	15 (39.5)	24 (50)
Absent	23 (60.5)	24 (50)
Abscess collection(s)		
Present	24 (63.2)	23 (47.9)
Absent	14 (36.8)	25 (52.1)
Data are given as mean \pm SD or n (%).		

In the 38 patients who underwent LST there were a total of 72 lesions and the number of lesions in individual patients ranged from 1–4. Of these 72 lesions, 70 (97.2%) were accepted as complete response, and two lesions were accepted as partial response in different sessions. The median largest dimension of the lesions was 23.50 (15.25–35.25) mm before treatment, which regressed to 16 (12–25) mm after the first session and to 11 (9–17) mm after the second session. The median change in maximum lesion dimension were 43.9 (25.1–69.6) percent in the first session. The degree of treatment responses, absolute change in millimetres and percentage changes of the measurements made after all sessions are shown in Table 2. In Group 1, when the treatment results were evaluated on a patient by patient basis, 8/38 patients recovered completely after the first session, six after the second session, 12 after the third session, 6 after the fourth session, and 4 after the fifth session. As a result, complete recovery was achieved in 36 (94.5%) of 38 patients. Two (5.5%) patients who were considered to have partial recovery were followed up without any treatment. These patients did not have any complaints during the 12-month follow-up and the lesions size remained stable. In Group 2, 37/48 (77.1%) patients received wide excision, 6 (12.5%) local excision, and 5 (10.4%) mastectomies.

Table 2
Treatment results according to the lesions

	Pre-treatment (n = 72)	1st session (n = 72)	2nd session (n = 55)	3rd session (n = 39)	4th session (n = 14)	5th session (n = 5)	Final results (n = 72)
Complete response	-	17	16	23	9	5	70
Partial response	-	0	0	2	0	0	2
Lesion size (mm) (25p-75p)	23.50 (15.25–34.25)	16 (12–25)	11 (9–17)	10.50 (8.25–14.75)	9 (8–11)	0 (0–0)	0 (0–0)
Percentage decrease of lesion size (25p-75p)	-	43.9 (25.2–69.6)	59.2 (50–100)	100 (68.4–100)	100 (75.5–100)	100 (100–100)	100 (100–100)
Data are given as n or median (25p-75p).							

In order to achieve a complete response, the median NoS was calculated as 2.00 (1.00–3.00) in 45 lesions of < 3 cm in size and 3.00 (2.00–4.00) in 25 lesions of ≥ 3 cm size ($p = 0.002$). There was no significant difference in terms of the NoS required between patients with one lesion ($n = 14$) and patients with two lesions ($n = 12$), as well as between the patients with two lesions and the patients with three or more lesions ($n = 10$) ($p = 0.672$ and $p = 0.230$, respectively). It was observed that a median of 3.00 (3.00–4.25) sessions was applied to 14 patients with fistula, while the median requirement was significantly less at 2.00 (1.00–3.00) sessions in 22 patients without fistula ($p = 0.002$). In terms of abscess presence, significantly more sessions with a median of 3.00 (3.00–4.00) sessions were applied to 22 patients with abscess compared to a median of 1.00 (1.00–2.00) session in 14 patients without abscess ($p < 0.001$).

In Group 1, 30 (79%) patients scored their pre-treatment pain between 7 and 10, and eight (21%) patients scored between 4 and 6 points. After the first session, only one patient reported a pain score of between 7 and 10, while 13 patients scored 0 points. In terms of post-treatment pain, 14 patients described their pain as mild and 24 patients described no pain. Median pain scores for Group 1 were 8.00 (7.00–10.00) before the treatment, 3.00 (0–4.00) after the first session, and 0 (0–1.00) after the treatment. There was a significant difference between pre-treatment and post-treatment scores, as well as between pre-treatment scores and scores after the first session (both $p < 0.001$). Before the treatment, 36 (75%) patients in Group 2 scored their pain between 7 and 10, six (12.5%) between 4 and 6, and six (12.5%) between 1 and 3 points. After the treatment, one patient described her pain as severe and 24 patients described it as moderate. Median pain scores for Group 2 were 8.00 (6.25–10.00) before the treatment and 4.00 (2.00–5.00) after the treatment, decreasing significantly ($p < 0.001$). While the pre-treatment pain scores of Group 1 and Group 2 were similar ($p = 0.756$), there was a significant difference in the post-treatment pain

scores with Group 2 reporting higher median pain scores than Group 1 ($p < 0.001$). The NPRS results of the groups are shown in Figure-1.

In Group 1, hematoma developed in two patients after injection. There were no steroid-related local or systemic side effects. In Group 2, surgical site infection developed in three patients and hematoma developed in one patient. Complication rates were calculated as 5.2% for Group 1 and 8.3% for Group 2 ($p = 0.690$). In Group 1, no recurrence developed in any patients in the first 12 months after the treatment. In Group 2, recurrence developed in 10 of 37 (27%) patients with wide excision and in 5 of 6 (83.3%) patients with local excision; in total 15 of 48 (31.2%) patients. Group 2 had significantly higher recurrence rates ($p < 0.001$). The median treatment costs of Group 1 and Group 2 were calculated as 21 (14–25) USD and 198.50 (171–275.75) USD, respectively. There was a significant difference between the treatment costs of the groups ($p < 0.001$).

Discussion

Autoimmunity, hormonal disorders and infection are among the most likely factors in the etiology of IGM. The most widely accepted hypothesis is that IGM develops as a result of an autoimmune process [2, 11, 12]. The results of our study support this hypothesis. The disease developed in the passive breast in more than 90% of our patients with a passive breast history. When breastfeeding in a lactating breast does not occur, ductal epithelium damage occurs because of milk stasis. Extravasation of secretions, as a result of ductal damage, cause macrophage and leukocyte migration into the tissue, triggering local inflammation [13–16]. Based on this information and our observations, we consider that ductal damage plays an important role in the pathogenesis of IGM, and that inflammation resulting from ductal damage due to any reason may lead to IGM.

On the assumption that the disease mechanism in IGM was autoimmune, steroid and other immunosuppressive agents have been used in its treatment and the disease was demonstrated to respond to these agents [11, 12]. However, common side effects, including myopathy, iatrogenic Cushing syndrome, hypertension, weight gain and hyperglycemia, may occur with systemic steroid use [17, 18]. These side effects may have a severe effect on quality of life and result in the patient requiring long-term treatment. Although the use of medical treatments for suspicious etiological factors, especially autoimmunity, is widespread, surgery is still a common treatment method. However, surgical applications can cause poor cosmetic outcomes, and recurrence rates after surgery are considerably higher, as in our study. In the treatment of benign diseases, the development of side effects that reduce the quality of life or result in poor cosmesis are undesirable. However, the possibility of experiencing these side effects after LST is negligible, in our experience.

The response of all lesions to steroid injection in our patients supports the hypothesis that IGM develops due to an autoimmune process. Özel *et al.* [19] found positivity in rheumatoid factor in 6 of 8 patients, and anti-nuclear antibody and anti-DNA antibodies in 2 of 8 patients with a diagnosis of IGM. In another study, Saydam *et al.* [20] reported a difference in serum interleukin 22 and interleukin 23 levels in

patients with (n = 26) and without (n = 15) a diagnosis of IGM, and stated that this difference supports an autoimmune etiology for IGM. However, data on this aspect of IGM are limited and further studies are needed on the presence of autoimmune markers in IGM.

The proportion of patients in whom a complete recovery was achieved following LST was gratifying, given that the optimal treatment for IGM is controversial. In addition, the findings in patients exhibiting partial recovery that the lesion size did not increase and the disease did not progress may be an indication that the steroid restricts the disease by suppressing active inflammation. In a similar study, Toktaş *et al.* [10] reported that 93.5% of the patients undergoing LST responded to the treatment. These results show that LST is an effective method in the treatment of IGM.

In the LST Group, the presence of a lesion ≥ 3 cm in size, fistula or abscess made treatment less effective and patients with these features generally required a greater NoS for successful treatment. In patients with a fistula, the treating physician was able to observe injected steroid leaking directly into the fistula, thus reducing the concentration in the lesion. In addition, in patients with an abscess, re-formation of abscess negatively affected the treatment process. In earlier studies classifying IGM, the disease was considered to be complicated in the presence of fistula and abscess [21–23]. The results of our study also support this view. In addition, our detailed size analysis showed that a lesion size of ≥ 3 cm prolonged the treatment process, and we suggest that lesions of these sizes should also be considered as complicating the disease.

One of the common symptoms of IGM is pain [1, 11]. To the best of our knowledge, our study is the first study evaluating pain intensity in IGM. The NPRS we used for this purpose is a sensitive and convenient tool in practice and has previously been used in many studies with high reliability [24]. More than 75% of our patients described their pain as severe before treatment, which highlighted the importance of pain relief as part of IGM treatment. Following the first LST session, reported pain regressed from severe to mild and reached tolerable levels soon after the first session in most patients. After completion of treatment, complete pain relief was reported by most, and no patient describing her pain as severe, suggesting that LST is very successful for pain management in IGM. Since the pain of most patients regressed to moderate and some continued to describe their pain as severe in surgical treatment, it can be concluded that LST is superior to surgery in pain management.

Steroids are known to have a wide range of side effects. However, intralesional and topical application, as used in the LST group, was found to be safe with no evident side effects. In contrast, Çetin *et al.* [25] reported local side effects in the breast skin in 24.4% and systemic side effects in 2.4% of patients due to usage of topical steroids. In addition, 38.2% of patients developed systemic side effects, such as hirsutism, weight gain and iatrogenic Cushing syndrome related to systemic steroid use. Toktaş *et al.* [10] also reported local side effects at a rate of 2.2% in their LST group, and systemic side effects at a rate of 9.4% in the group treated with systemic steroids. It is notable that systemic treatment was not reported to be superior to local applications in terms of treatment efficacy in either of these studies. As a result, we

suggest that local applications of steroids should be used in the treatment of IGM, as localized side effects can be easily managed when compared to side effects from systemic treatment.

Recurrence rates after surgical treatment are high in IGM, with rates in the literature generally reported to be between 5% and 50% [1, 11, 13, 26] although the highest recurrence rate after surgery was 72.7% [27]. We suggest that local excision should be avoided in the treatment of IGM, since 83.3% of patients with local excision had recurrence in our study. Occurrence of relapse in patients undergoing wide excision with apparent negative margins may be an indication that the inflammation had affected more tissue than could be detected. In contrast, the absence of recurrence in LST may indicate that the steroid suppresses active inflammation completely. Moreover, resection in IGM can cause undesired cosmetic results [8, 10, 28]. Due to high recurrence rates and poor cosmetic results, patients may require multiple operations and some of these patients even require mastectomy [29]. These cosmetic problems also lead to psychological problems [29, 30]. The probability of cosmetic problems in LST is relatively lower.

Our study has several limitations. First, it is a retrospective study with a limited number of patients. Second, the follow-up period was insufficient in terms of recurrence risk. Third, there is a scarcity of data in the literature concerning LST and no defined treatment protocol is recommended. Therefore there is a requirement for long-term follow-up studies involving larger patient groups, which would yield more data about treatment efficiency and recurrence rates following LST. These studies could also help to identify the optimal protocol for LST.

Conclusion

The most likely hypothesis is that IGM is an autoinflammatory disease. Based on this hypothesis and the results of our study, we believe that suppressing inflammation in patients with IGM rather than resection is a more effective and acceptable treatment. LST, a treatment method with high efficiency, low recurrence rate, low cost and without cosmetic loss, should be the first option to be used in all IGM patients, including cases complicated by fistula or abscess.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

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Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Ethics approval: This study was approved by the local ethics committee of our institute (Reg. Number: GOKAEK2020/282).

Consent to participate: As this was a retrospective study, informed consent was deemed not to be necessary from the patients.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figure 2.

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Figures

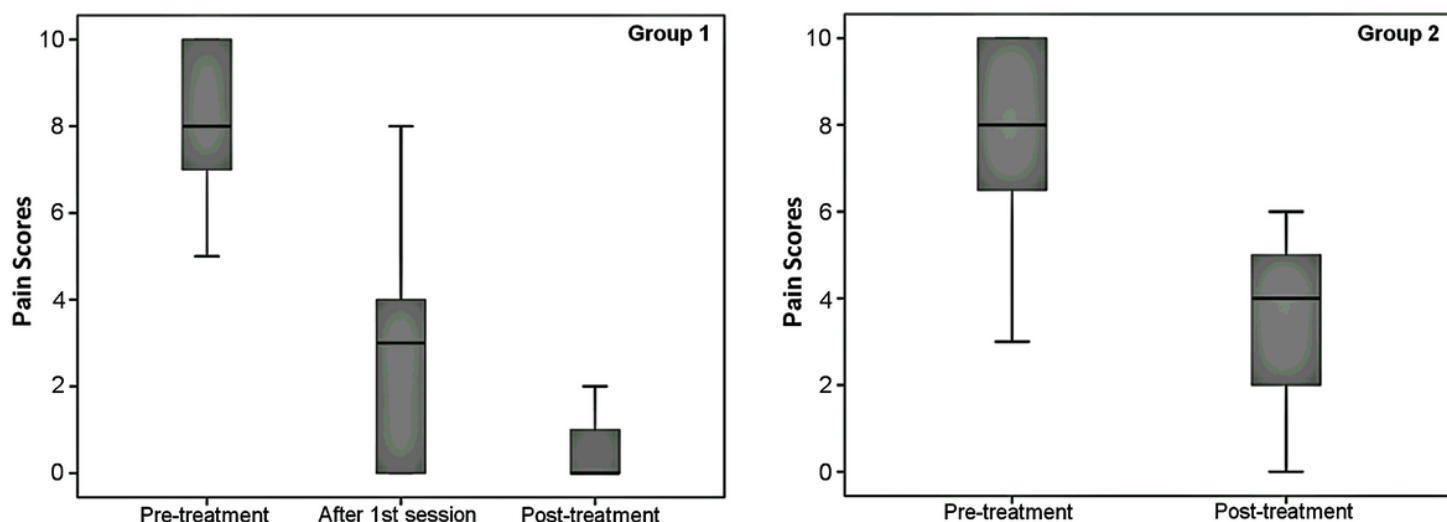


Figure 1

Box-plot graphs of patient reported pain scores (NPRS) for each group Pain of the patients was reported at tolerable levels after the first session in Group 1 (LST group). Even after the first session in the LST

group, pain was reported to be less intense than after completion of treatment in the Group 2 (surgery group).



Figure 2

Clinical images before and after LST in a patient with a three previous surgical interventions for IGM a The patient had abscesses, fistula formation, nipple retraction, hyperemia and scars due to previous surgeries. b After five sessions, the patient completely recovered. Only surgical scars remained on the breast skin.

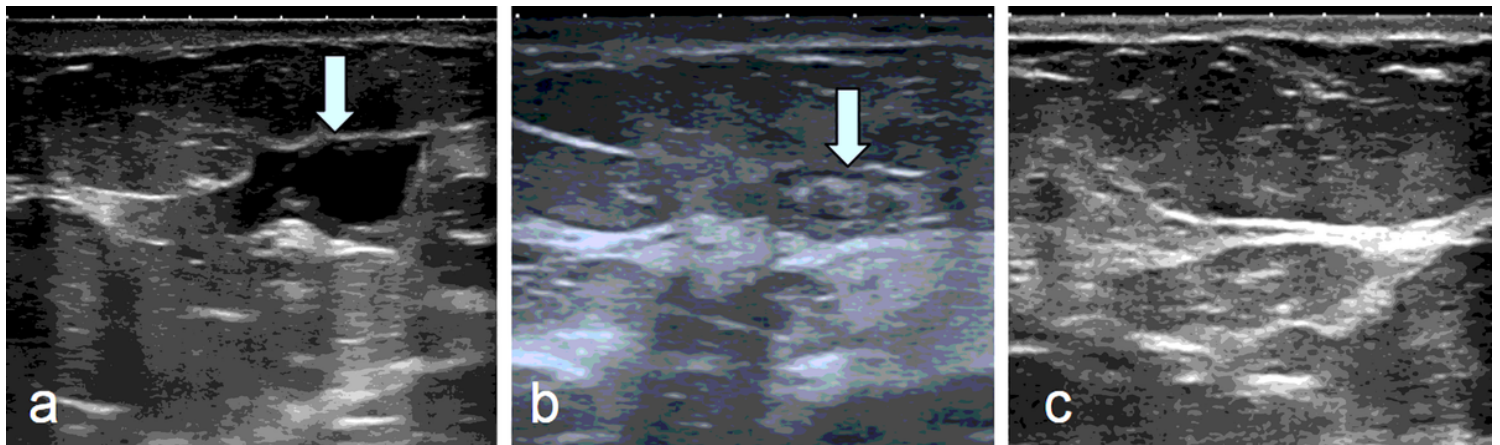


Figure 3

USG images of a patient before and after LST 38-year-old woman, presented with a painful breast mass. Percutaneous biopsy showed non-necrotizing granulomatous inflammation. Pre-treatment USG image (a) demonstrates a regular, hypoechoic mass with angular margins. The largest dimension of the lesion was 24 mm before treatment, which regressed to 10 mm after the first session (b). The lesion is indicated by an arrow in both images. Following two sessions at 1-month intervals, complete response of lesion in post-treatment USG image (c) was evident.