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ORIGINAL SCIENTIFIC REPORT

Comparison of Topical, Systemic, and Combined Therapy with Steroids on Idiopathic Granulomatous Mastitis: A Prospective Randomized Study

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Abstract

Background Idiopathic granulomatous mastitis (IGM) is a benign disorder of the breast, for which the optimal treatment modality remains missing.

Methods A total of 124 patients with a histopathologically proven diagnosis of IGM were enrolled in a prospective, randomized parallel arm study. Patients were treated with topical steroids in Group T (*n*: 42), systemic steroids (0.8 mg/kg/day peroral) in Group S (*n*: 42), and combined steroids (0.4 mg/kg/day peroral + topical) in Group C (*n*: 40). Compliance with the therapy, response to the therapy, the duration of therapy, side effects and the recurrence rates were compared.

Results Sixteen patients did not comply with the treatment, and the highest ratio of compliance with therapy was seen in Group T ($p < 0.05$). Complete clinical regression (CCR) was observed in 90 (83.3%) patients. Response to the treatment (RT) was evaluated radiologically and observed in 89.8% of the patients. There was no statistically significant difference between groups regarding CCR, RT and the recurrence rate. The longest duration of therapy was observed in Group T (22 ± 9.1-week), whereas the shortest was observed in Group S (11.7 ± 5.5-week) ($p < 0.001$). The systemic side effects were significantly lower in Group T in comparison with Groups S and C (2.4% vs. 38.2% and 30.3%, respectively) ($p < 0.001$).

Conclusions The efficiency of the treatment was similar for all groups, both clinically and radiologically. Although the duration of therapy was longer in Group T, the lack of systemic side effects increased the compliance of the patients with the therapy. Therefore, topical steroids would be among first-line treatment options of IGM.

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Introduction

Idiopathic granulomatous mastitis (IGM) is a benign chronic inflammatory disorder of the breast [1]. Inflammatory skin, a palpable mass with pain, fistula, ulcerations, and abscess are the most common signs. The exact incidence is unknown, and it usually affects women of childbearing age [2]. Considering the literature, it seems to be a problem that mainly affects Asian and North African populations, including Turkey [3]. Non-caseating granulomas in breast lobules during histopathological examination confirm the diagnosis. In addition, granulomatous disorders, either infectious or non-infectious, should be excluded to confirm IGM.

The optimal treatment modality remains missing due to unknown etiology. Surgical excision, steroids, and methotrexate have been found to be satisfactory in retrospective studies. However, the side effects and recurrence rates for medical treatment and insufficient cosmetic results for surgical treatment remain obstacles in search of an ideal therapy. There was no prospective randomized study on the ideal approach for the treatment. In contrast to the literature, the effectiveness of the treatment with topical steroids has been reported for twice consecutively by a single center, a few years ago [4, 5].

The major aim of the study was to compare topical, systemic, and combined (topical + systemic) steroid therapy regarding their effectiveness and side effects in the management of IGM.

Materials and methods

Design and subjects

This study was planned as a prospective, randomized parallel arm study.

IGM patients who were admitted to the breast unit in Kartal Dr. Lütfi Kırdar Training and Research Hospital, Istanbul, were planned to be recruited for this study. All clinical evaluations, treatments, and follow-ups were performed by two experienced breast surgeons. The diagnosis of all patients was carried out by histology, imaging, and physical examination. The patients were only admitted to the study after exclusion of other etiologies such as infections and other autoimmune diseases.

Diagnosis of IGM

All patients had core biopsies for both histopathological and microbiological evaluation. Biopsies for microbiological evaluation—Gram, periodic acid-Schiff and Ziehl–Neelsen staining, mycobacterial cultures and fungal analysis with Grocott–Gomori methenamine silver staining—were performed at the same time. In addition, following the diagnosis, purified protein derivative skin test (PPD) and QuantiFERON test were performed to exclude tuberculous mastitis. Patients with a suspicious or positive result were verified with PCR for Mycobacterium.

Inclusion and exclusion criteria

Only those patients with a clinical and histologic diagnosis of granulomatous mastitis were included in the study. Other histopathological diagnoses and positive culture for mycobacteria and fungus were among the criteria for exclusion.

All patients were informed in detail before the treatment, and informed consent from the patients was taken. The study was approved by the local ethics committee of our institute (Reg. Number 51414003).

Randomization and study (treatment) groups

A web-based table was conducted before the study to randomize into three treatment groups: Group T (topical steroid), Group S (systemic steroid), and Group C (topical + systemic steroid).

Group T Prednasinolone 0.125% pomade (Prednol pomad; Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey) was applied to the affected breast, twice a day. A stretch film was applied for an hour to avoid the reduction of absorption. The demonstrative application of topical treatment was shown at the hospital, and the remaining applications were done by the patients at home. Prednasinolone was applied for the weekdays, with breaks during weekends (1-week cycle). Treatment of the cycles was continued in the form of weekly cycles until CCR was obtained.

Group S Patients received oral methylprednisolone (16 mg and 4 mg) (Prednol tablet; Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey). Postprandial 0.8 mg/kg was applied at the morning for once and tapered slowly according to the clinical and radiological response.

Group C Combined therapy of Group T and Group S was applied for the patients. In contrast to Group S, oral methylprednisolone was applied 0.4 mg/kg in Group C, and it was tapered slowly according to the clinical and radiological response.

Superficial abscesses with fluctuation were drained either on admittance or during the treatment in all groups.

Outcomes

The efficiency of each treatment arm was the main outcome of the study. This was measured through both symptomatic and radiological assessments. Side effects of each of the treatments and patient compliance were the secondary outcomes.

Assessment of response to treatments

Improvement of fistula and ulcerations, the disappearance of palpable lesions, and the regression of inflammatory findings were defined as complete clinical regression (CCR) (Fig. 1). Radiological evaluation with ultrasonography (US) and magnetic resonance imaging (MRI) was performed before the treatment and during the treatment for periods of 3 months and before the termination of treatment. Considering the radiological evaluation, partially or advanced regression was defined as incomplete radiological regression (IRR), and the disappearance of radiological findings was defined as complete radiological regression (CRR) (Fig. 2). Patients with CRR and IRR were defined as being responsive to the treatment (RT), whereas the progression or absence of improvement during the treatment regarding clinical and radiological findings was defined as unresponsive to treatment (URT). Patients who do not participate in regular follow-ups, lost to follow-ups, or did not participate in medical therapy regularly due to side effects and patients who want surgery during medical treatment were defined as treatment incompatibility (TIC).

Patients were accepted as URT, in case of clinical and radiological progression at controls during the treatment and stable lesions despite treatment for three months.

Treatment endpoints

CCR or URT during the treatment and the occurrence of any systemic side effects other than weight gain and hirsutism were the endpoints of the treatment, in all groups. The duration of treatment was not predetermined with a limitation to determine the recovery period of topical treatment. Considering our daily practice and experience, systemic steroid therapy more than 6 months in Groups S and C was avoided to prevent the development of iatrogenic Cushing, in the case of a recovery period longer than 6 months.

Data

Patient characteristics and demographics, duration of the disease, previous diagnosis, and the treatment, findings of physical examination, imaging, and pathology were recorded prospectively.

Follow-up

The patients were controlled every 2 weeks during the treatment. The weight of the patients was measured before and during the treatment. Side effects of the topical therapy such as skin thinning, secondary infections, hyperpigmentation, and telangiectasia were assessed during each visit. Weight gain—more than 5% following treatment,

Fig. 1 Clinical evaluation of affected breasts and RT. **a** 41-year-old patient with BIRADS 4 mammogram, three quadrants were affected. **b** Appearance following topical treatment, drying, thinning and telangiectasia was observed. **c** The patient was accepted as CCR and CRR after 24 weeks of treatment. **d** 31-year-old patient with previous ciprofloxacin therapy. Multiple lesions with fistula affecting two quadrants. **e** The patient was accepted as CCR and CRR following the systemic treatment of 2 months. **f** The appearance of the breast after 6 months

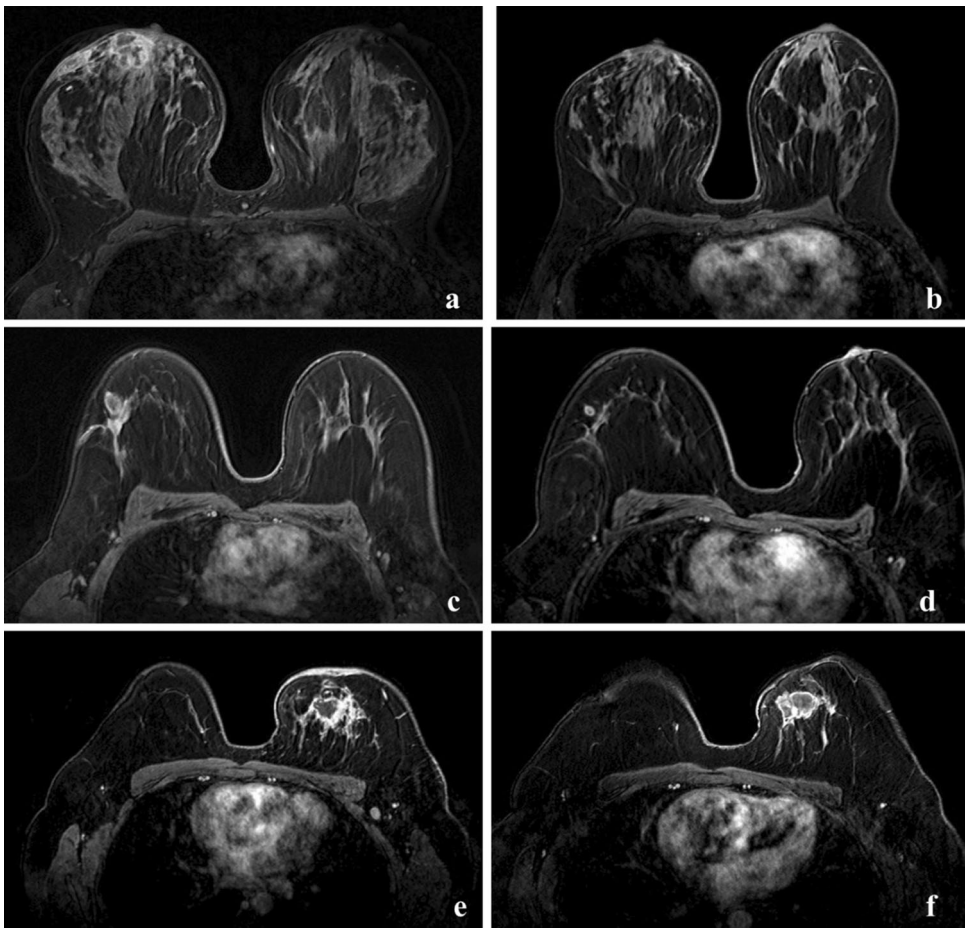

Fig. 2 The radiological appearance of lesions and evaluation of RT. **a** The lesion is containing necrosis with heterogeneous contrast enhancement at the retroareolar region of the right breast. **b** The lesion was disappeared following treatment and accepted as CRR. **c** Abscess formation at the right breast before treatment. **d** The decrease in the size of the lesion was observed following treatment and accepted as IRR. **e** The lesion is containing a central necrotic area at mid-internal localization of left breast. **f** Increase in the size of the lesion was observed following treatment and accepted as URT

hirsutism, and other cushingoid symptoms were recorded as systemic side effects. Following the termination of treatment, the patients were assessed, during the 1st, 3rd, and every 6 months thereafter. Recurrence was accepted in case of recurrent lesions with radiological verification of the same breast during the follow-up of the patients with RT.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Descriptive statistical methods were used to evaluate the study data. The Pearson Chi-square test and the Fisher's exact test were applied to compare qualitative data. The normality of data distribution was assessed by the Kolmogorov–Smirnov test. One-way ANOVA and the Kruskal–Wallis test were used to compare quantitative variables for the groups with and without normal distribution, respectively. Based on the results of analyses, the p value < 0.05 was considered to be statistically significant.

Results

Cohort

A total of 165 patients who were diagnosed with IGM (between September 2014 and November 2017) were eligible for the study. Patients who did not want to participate in the study (n: 4), had an obstacle with using steroids (diabetes n: 3, impaired fasting glucose n: 7), preferred surgical treatment (n: 6), were diagnosed with tuberculosis during the evaluation (n: 5), or experienced a recurrence following the treatment with steroids previously (n: 16) were excluded. Following the exclusions, 124 patients with IGM were randomized to 3 groups as follows: topical treatment (Group T; n: 42), systemic treatment (Group S; n: 42), and combined treatment (Group C; n: 40). Selection of the patients is depicted in Fig. 3 as a flowchart.

All the patients were female with a mean age of 33.9 ± 6.8 (within a range of 20–58), and 120 (96.8%) of them were in the premenopausal period. 78 (62.9%) patients had a history of previous antibiotic treatment for IGM (median: 4 weeks, range 1–12). All patients who

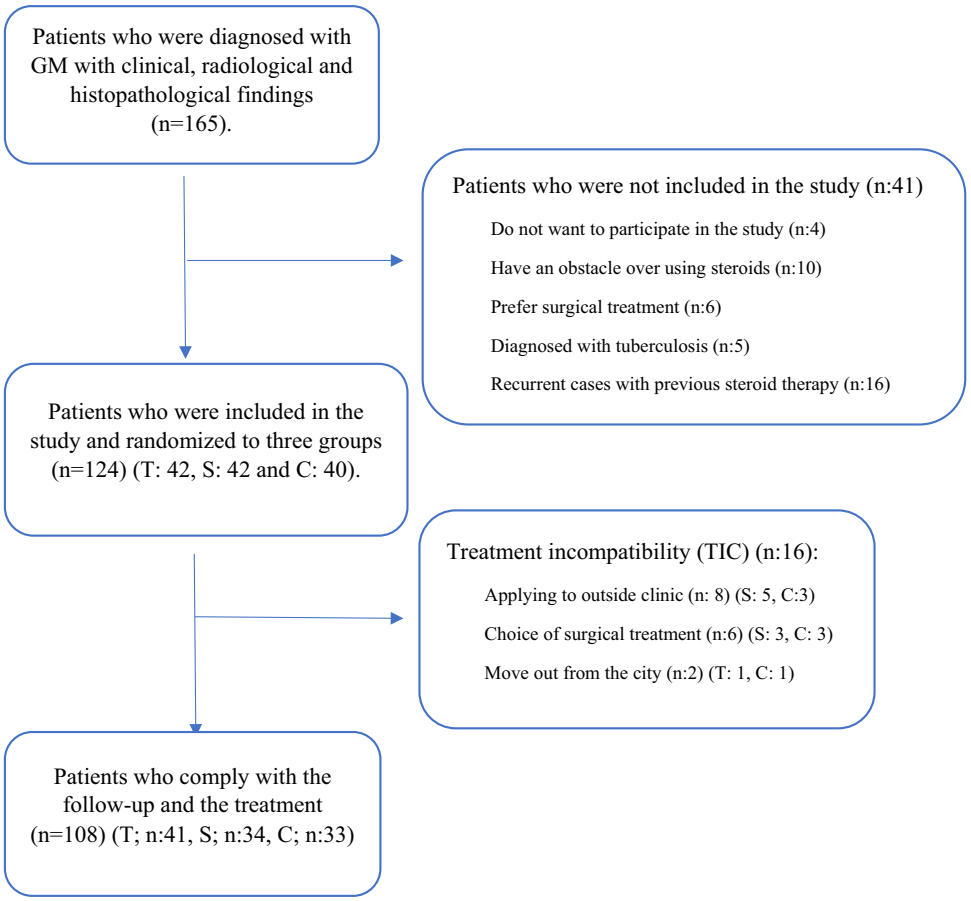

Fig. 3 Selection of patients with IGM

received antibiotics were referred from other clinics. Twenty-two (17.7%) patients had a superficial abscess, and drainage was applied at admittance. There was no statistically significant difference between groups, regarding the age, the rate of antibiotic therapy, the distribution of affected quadrants, fistula, skin ulcerations, and the presence of an abscess. In addition, randomization between groups was similar regarding the longest diameter of the lesions detected in the MRI and US. The demographics of the patients in accordance with the groups and clinical findings are depicted in Table 1.

Sixteen (12.9%) of 124 patients didn't comply with the treatment due to various reasons—choice of surgical treatment (*n*: 6), visiting another clinic (*n*: 8), moving out of the city (*n*: 2)—and were accepted as TIC (Fig. 3). The TIC was more in Groups S (*n*: 8) and C (*n*: 7), in comparison with Group T (*n*: 1) ($p < 0.05$). Following the exclusion of 16 patients with TIC, the clinical and radiological success of treatment, duration of therapy, follow-up time, recurrence rate and the side effects were evaluated in the remaining 108 patients (Group T; *n*: 41, Group S; *n*: 34 and Group C; *n*: 33) (Table 2).

The durations of the treatments in each group were significantly different ($p < 0.001$). The longest duration of treatment was observed in Group T (22 ± 9.1 weeks). The shortest duration of the treatment was seen in Group S (11.7 ± 5.5 weeks) (Table 2). The mean overall follow-up time after the completion of the treatment was 94 ± 28 (range 55–191) weeks. There was no statistically significant difference between the mean follow-up durations of Groups T, S, and C (92 ± 31, 97 ± 24 and 95 ± 28, respectively).

Treatment response

Complete clinical regression was observed in 83.3% (90/108) of the patients, and the rate was close between Groups T, S, C (82.9%, 85.3%, 81.8%, respectively) ($p = 0.93$). Considering the radiological response, CRR was observed in 56.5% (61/108) and IRR was observed in 33.3% (36/108) of the patients. The highest rate of CRR was observed in Group S (61.8%). The response to the treatment (RT) was evaluated radiologically in our present study. RT was observed in 89.8% (97/108) of the patients who complied with the treatment, and there was no statistically significant

Table 1 Demographics, clinical characteristics, and presentation, the outcome of 124 patients with IGM in accordance with treatment modalities

	All patients (*n*: 124)	Group T (*n*: 42)	Group S (*n*: 42)	Group C (*n*: 40)	*p* value
Age (year, mean ± SD.)	33.9 ± 6.8	34.0 ± 6.1	33.6 ± 7.3	33.9 ± 7.1	0.97
Premenopausal (*n*/%)	120/96.8	40/95.2	41/97.6	39/97.5	0.79
Use of antibiotic (*n*/%)	78/62.9	24/57.1	27/64.3	27/67.5	0.61
Time, week (median/range)	4/1–12	4/1–8	4/1–8	4/2–12	0.72
Side (*n*) (right/left/bilateral)	65/55/4	18/24/0	25/14/3	22/17/1	0.12
Affected quadrant[a]					
Single (*n*/%)	71/57.3	24/57.1	27/64.3	20/50	
Double (*n*/%)	36/29	12/28.6	11/26.2	13/32.5	0.74
> 2 quadrants (*n*/%)	17/13.7	6/14.3	4/9.5	7/17.5	
Presence of fistula					
No (*n*/%)	95/76.6	34/81	33/78.6	28/70	
Single (*n*/%)	24/19.4	6/14.3	8/19	10/25	0.74
Multiple (*n*/%)	5/4	2/4.7	1/2.4	2/5	
Presence of ulcer (*n*/%)	23/18.5	8/19	6/14.3	9/22.5	0.63
Presence of abscess					
No	44/35.5	15/35.7	15/35.7	14/35	
Radiological (USG, MRI)	58/46.8	23/54.8	17/40.5	18/45	0.47
Superficial fluctuating	22/17.7	4/9.5	10/23.8	8/20	
Mean mass size, mm (range)[b]	33.3/10–85	33.6/10–85	31.4/10–75	35/10–75	0.63

[a]The most affected breast was evaluated in case of bilateral disease (*n*: 4)

[b]Longest diameter of the largest lesion radiologically (USG and MRI) described

Table 2 Comparison of groups in accordance with the follow-up time, duration of therapy, clinical and radiological response, and recurrence rate

	All patients (*n*: 124)	Group T (*n*: 42)	Group S (*n*: 42)	Group C (*n*: 40)	*p* value
TIC (*n*/rate, %)	16/12.9	1/2.4	8/19	7/17.5	0.04
Overall RT (*n*/rate, %)	97/78.2	37/88.1	31/73.8	29/72.5	0.16
Patients with compliance to treatment:	All patients (*n*: 108)	Group T (*n*: 41)	Group S (*n*: 34)	Group C (*n*: 33)	
CCR (*n*/rate, %)	90/83.3	34/82.9	29/85.3	27/81.8	0.93
Radiological response (*n*/rate, %)					
CRR	61/56.5	22/53.7	21/61.8	18/54.5	0.95
IRR	36/33.3	15/36.6	10/29.4	11/33.3	
URT	11/10.2	4/9.8	3/8.8	4/12.1	
RT (*n*/rate, %)	97/89.8	37/90.3	31/91.2	29/87.9	0.90
Abscess drainage (*n*/rate, %)[a]	35/32.4	13/31.7	7/20.6	15/45.5	0.09
Recovery period, week (mean ± SD/range)	16.8 ± 8.6/4–44	22 ± 9.1/8–44	11.7 ± 5.5/4–24	15.6 ± 6.9/4–28	< 0.001
Follow-up time, week (mean ± SD/range)	94 ± 28/55–191	92 ± 31/55–191	97 ± 24/57–145	95 ± 28/62–161	0.70
Recurrence (*n*/rate, %) (median month after initial treatment/range)	17/18.9 (5.5/2–39)	5/14.7 (8.5/7–39)	6/20.7 (3/2–9)	6/22.2 (4/3–12)	0.54

TIC treatment incompatibility, *RT* responsive to treatment (CRR + IRR), *CCR* complete clinical remission, *CRR* complete radiological regression, *IRR* incomplete radiological regression, *URT* unresponsive to treatment—patients with radiologically progressive or stable

[a]During treatment

difference between groups regarding the radiological response (90.3%, 91.2%, and 87.9%, in Groups T, S, and C, respectively) ($p = 0.9$). Although there was no significant difference even in the case of including the patients with TIC (*n*: 16), the rate of overall RT was higher in Group T (88.1%) in comparison (Table 2). There was no

Table 3 Comparison of groups in accordance with side effects

Side effects	In all pat. (*n*: 108)	Group T (*n*: 41)	Group S (*n*: 34)	Group C (*n*: 33)	*p* value
Patients with local side effects[a]	17 (15.7%)	10 (24.4%)	–	7 (21.1%)	0.75
Secondary skin infection—cellulitis	3 (2.8%)	1 (2.4%)	–	2 (6.1%)	
Skin thinning/drying/telangiectasia	14 (13%)	9 (22%)	–	5 (15.2%)	
Patients with systemic side effects	24 (22.2%)	1 (2.4%)	13 (38.2%)	10 (30.3%)	< 0.001
Weight gain ± hirsutism	21 (21.3%)	1 (2.4%)	11 (32.4%)	9 (27.3%)	
Iatrogenic cushing	3 (2.8%)	–	2 (5.9%)	1 (3%)	

[a]Statistical analysis was carried out only in the groups with the observation of side effects

statistically significant difference between the Groups T, S, and C regarding the recurrence rate, and the recurrence rates were found to be 14.7%, 20.7%, and 22.2%, in Groups T, S, and C, respectively.

Surgery was performed for the patients who were accepted as URT (*n*: 11) and TIC (*n*: 6, patients who preferred surgical treatment during steroid therapy). Types of surgeries were wide surgical excision (*n*: 14), simple mastectomy + latissimus dorsi myocutaneous flap (*n*: 2), and bilateral simple mastectomy + bilateral latissimus dorsi myocutaneous flap (*n*: 1). A re-excision was performed in 2 out of 14 patients with previous wide surgical excision owing to the recurrence. (Subareolar excision was performed).

Side effects

Considering the local side effects due to topical treatment, there was no statistically significant difference between Groups T and C ($p = 0.75$). However, systemic side effects were significantly lower in Group T in comparison with Groups S and C (2.4% vs. 38.2% and 30.3%, respectively) ($p < 0.001$). In the comparison of all side effects (both systemic and local), the most affected group was Group C (51.5% in Group C, 26.8% in Group T and 38.2% in Group S). Iatrogenic Cushing was the most severe side effect and affected 2.8% of all patients (2 patients in Group S and one patient in Group C). The long period of oral steroid therapy was related to this condition (16 and 24 weeks in Group S, 28 weeks in Group C). The side effects are shown in Table 3, in detail.

Discussion

Since IGM was first described in 1972, consensus on the treatment remains missing. The most preferred methods in daily practice are surgical excision, systemic (oral) steroids, and surgical excision following systemic steroids [6–8]. To the best of our knowledge, this is the first study comparing topical therapy with systemic therapy and evaluating the efficiency of combined therapy. The efficiency of the treatment was similar for all groups, both clinically and radiologically. However, compliance with the therapy in Group T was higher than in the remaining groups ($p < 0.05$). In addition, fewer complications were observed with topical treatment, as most of the side effects were mild and limited with the applied area, in comparison with systemic therapy. The systemic side effects could not be reduced significantly with the decreased dose of systemic steroids in combination with topical treatment. The prolonged duration of treatment in the combined group could be responsible for this condition. The local side effects were also observed due to topical treatment in this group. Hence, the highest rate of side effects was observed in the combined group (51.5% of the patients).

Satisfactory results in two limited series (*n*: 11 and *n*: 28, respectively), following topical treatment with steroids, were reported by the same department consecutively in 2014 and 2015 [4, 5]. Topical steroids were applied for up to 12 weeks for patients with skin lesions without abscess. CCR was reported for all patients with no side effects. The recurrence rates were found as 18.2% and 10.7% with a minimum follow-up of 12 months, respectively. Differently from the existing studies, RT was also evaluated radiologically in our study for an objective evaluation. The patients who have progression or do not have improvement radiologically were accepted as URT. In Group T, our mean duration of therapy is longer (22 weeks), and CCR is lower (82.9%) than existing studies, which could be the result of randomization without patient selection. Patients with abscess formation and extensive diseases who tried to be treated with topical therapy could explain this situation. The recurrence rate was 14.7% (5/34) with a mean follow-up of 92 (55–191) weeks for the patients with CCR in Group T. However, we observed side effects in Group T with a ratio of 26.8% (Table 3). The retrospective design of previous studies and short duration therapy could be explanatory for contradictory results.

The mean recovery period of the disease with systemic therapy was reported between 3 and 5 months, and the most dangerous complication was the systemic side effects owing to long-time therapy [9, 10]. The mean recovery period was 11.7 ± 5.5 weeks for Group S with a dose of 0.8 mg/kg/day, in our series. Complete remission rates were in a range between 72 and 86.4%; the recurrence rate was in a range between 5.5 and 22.7% with oral steroids [10–12]. The CCR was 85.3%, and the recurrence rate was 20.7% with 97 (57–145) weeks of mean follow-up in Group S, in a similar fashion with these studies.

The skin, subareolar region and more than a single quadrant were affected in many of the patients with IGM, and it is impossible to perform a surgery with better cosmetic results, in daily practice [13]. High recurrence rates (23–50%) were reported for limited excisions, which avoid poor cosmetic results [2, 14]. IGM affected more than one quadrant in 42.7% of the patients, in our series. Repetitive surgical excisions, even mastectomy, and reconstructive procedures could be required simultaneously during the treatment of these patients [15, 16]. IGM is a benign disease which affects women who are at the childbearing age, and regression was reported even without treatment [17, 18]. Therefore, it is essential to protect the breasts and breastfeeding functions of these young patients, and we use surgery only in case of a limited disease with a single quadrant or localized lesions as first-line treatment.

Conservative treatment had been reported to be sufficient for selected cases, with or without drainage, previously [17, 18]. These two studies were retrospective, and most of the cases presented with mass and without an open wound. In addition, contradictory results regarding the complete resolution rate and mean interval were remarkable. The prospective study design, including an arm of observation, had been suggested previously [19]. However, our unit is a tertiary referral center, and most of the cases were referred from other regional hospitals after unsuccessful treatment, previously. Although there were no cases with previous steroid therapy in our series, the antibiotic therapy rate with or without surgical intervention before admission was 62.9% (*n*: 78). Therefore, conservative treatment was not an option for these patients. Also, a recent meta-analysis by Lei et al [8] was supportive for the treatment either with surgery or oral steroids.

In conclusion, the efficiency of topical treatment with steroids is similar to systemic and combined therapies. Although the recovery period became shorter with the high dose oral therapy, displeasing side effects impaired patients' compliance with therapy. Therefore, topical steroids would be among first-line treatment options of IGM.

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Compliance with ethical standards

Conflict of interest Author K.Ç. declares that he has no conflict of interest. Author H.E.S. declares that he has no conflict of interest. Author N.E.G. declares that he has no conflict of interest. Author G.R. declares that she has no conflict of interest. Author N.Ö.B. declares that she has no conflict of interest. Author H.F.K. declares that he has no conflict of interest. Author B.M.G. declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by Dr. Lutfi Kirdar Kartal Research and Training Hospital in affiliation with the University of Health Sciences' ethics committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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