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The Novel Treatment for Granulomatous Mastitis

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Comparison of the efficiency of systemic therapy and intralesional steroid administration in the treatment of idiopathic granulomatous Mastitis. The Novel Treatment for Granulomatous Mastitis

BACKGROUND: *Idiopathic granulomatous mastitis that has not had a clear consensus about its treatment since the day it was identified as a rare, benign inflammatory breast disease that mimics malignancy due to its appearance features.*
AIMS: *In our research, we intended to compare the efficiency of intralesional and systemic steroids administration in the treatment of idiopathic granulomatous mastitis.*
STUDY DESIGN: *Prospective randomized controlled study.*
METHODS: *A total of 36 female patients who had been histopathologically diagnosed with idiopathic granulomatous mastitis and whose other factors had been microbiologically excluded were included in the study. The patients were randomized into two sub-groups that would be treated with systemic and intralesional steroids. All patients were evaluated through physical examination one week after the completion of the treatment. Subsequently, the follow-up of the patients was performed thorough physical examination and ultrasonography and/or magnetic resonance imaging at the 1st, 3rd, and 6th months.*
RESULTS: *All patients adapted to treatment. Complete clinical regression occurred in 32 patients, while 30 of 36 patients responded to treatment both radiologically and clinically. A total of 4 patients had minor side effects. It was determined that there was no statistically significant difference between local and systemic steroid groups in terms of complete clinical regression, responded to treatment side effects, and recurrence rates.*
CONCLUSION: *Intralesional steroid administration was also considered just as a successful treatment method as the systemic steroid administration.*

KEY WORDS: Idiopathic granulomatous mastitis, Intralesional steroid, Systemic steroid

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare, benign inflammatory breast disease with unknown etiology that mimics breast cancer. It was first described by Kessler and Wolloch in 1972 upon evaluating the clinical and pathological findings of five patients with the symptoms of mastitis [1]. There are theories in the etiology suggest that protein secretion develops from the ducts secondary to trauma, infection, or mechanical stimulation, and that it is an autoimmune reaction related to this [2]. Typically, it occurs in younger females within a few years in the postpartum period, Asian and Hispanic populations being known to be the most commonly affected [1,3].

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IGM has clinical and radiological characteristics that mimic malignancy or acute breast infection [4]. The abscess clinic frequently co-exits, though it generally manifests itself as a painful, inflammatory mass in one breast [5]. Biopsy is necessary for definitive diagnosis. In addition to histopathological examination, the biopsy should be sent to gram stain test, bacterial culture analysis, acid-fast bacilli stain and culture, fungal stain, and culture analysis. Biopsy findings are typically characterized by non-necrotizing granulomas concentrated in lobules. Bacteria and fungi do not occur in granulomas at such an extent that the infective incident might be excluded [6].

No consensus regarding the optimal treatment of IGM has been reached yet because of the lack of prospective studies and fewer must be changed instead of the low number of cases. Typically patients presenting with mastitis at the beginning are prescribed antibiotics. Later when the diagnosis is established, they receive either systemic or topical steroids, or methotrexate, and sometimes they undergo surgical treatment [7,8].

Systemic corticosteroid therapy and extensive excision are the most frequently reported treatment methods in the literature, and most of the existing literature suggests that these treatments are effective [7,8].

However, the steroids which are commonly administered in the treatment, have many well-documented adverse effects such as peptic ulcer, edema, hypertension, diabetes, muscle atrophy, impaired wound healing, weight gain, hirsutism, and allergic reactions. Injections of intralesional steroids could be considered to lessen these adverse effects, accelerate the healing process and enhance the efficiency of the medication. Nowadays, intralesional corticosteroid therapy is successfully practiced in the treatment of acute and chronic inflammatory processes, hyperplastic and hypertrophic skin disorders, psoriasis, keloids, and typically in cases that respond positively to systemic and topical corticosteroids [9].

The most common adverse effects of the intralesional corticosteroid injections include skin atrophy, hypopigmentation, and rarely the formation of a sterile abscess. Atrophy and pigment change generally disappear in a couple of weeks. Administration of the corticosteroid at low concentrations and low doses dwindles the rate of complications [10].

In our study we aimed to compare the outcomes of intralesional steroid application with systemic application in the IGM treatment in terms of treatment efficacy, side effects, and recurrence rate.

Materials and Methods

Design and Subjects

The research was designed as a prospective randomized-controlled study. Patients who were diagnosed with IGM as histopathologically at the breast unit of the Health Sciences University Turkey, Gaziosmanpaşa Training and Research Hospital were included in the study. Prior to the study, approval was obtained from our hospital's local ethics committee (reg.: 162). Our study has been registered to ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT 04596046). All clinical assessments, treatments, and follow-ups were performed by a single breast surgeon and by a single radiologist.

The diagnosis of all patients was carried out through physical examination, imaging, and histopathology. Prior to the treatment, microbiological analysis was conducted concurrently with the biopsy. Gram, periodic acid-Schiff and Ziehl-Nelson staining culture, tuberculosis culture, tuberculosis polymerase chain reaction (Tbc PCR), acid-resistant bacterial culture (ARB culture), fungal staining (Grocott-Gomori methenamine-silver staining) and culture were studied in biopsy materials.

Inclusion and Exclusion Criteria

Only patients who had been diagnosed with IGM clinically and histologically were included in the study. Other causes, such as infections and autoimmune diseases, were excluded before patients were included in the study. Patients who had contraindications with the use of steroids, those with active infections, as well as patients who were pregnant, and who had been diagnosed with breast cancer, were not included in the study.

Initially, amoxicillin 875 mg + clavulanic acid 125 mg (Augmentin-BID 1000 mg tablet; GlaxoSmithKline, Istanbul) was administered two times a day for at least one week to all patients who applied with the manifestation of active infection. Percutaneous or surgical drainage procedure was performed on the patients who had an abscess in their breasts. Following the regression of active infection manifestations (fever, hyperemia of the breast, febrility, and abscess) the patients were re-evaluated through ultrasonography and informed about the treatment process, and their written consent was obtained.

Randomization and Study Groups

The patients were subdivided into two groups as Group S (systemic-peroral steroid) and Group L (local-intralesional steroid) by using the sealed envelope randomization method.

Group S: Medication of oral methylprednisolone (Prednol tablet; Mustafa Nevzat Medicines, Istanbul, Turkey) was administered to the patients following the adjustment based on the severity of the lesion and regarding the clinic. The prednisolone dose was 0.5 mg/kg/day in patients with painful, small (<5.0 cm) unilateral lesions whereas in multiple, bilateral lesions with the diameter of ≥5 cm or for those who had significant cutaneous

ulceration, the prednisolone dose was specified as 1 mg/kg/day [11,12]. Patients were informed about potential adverse effects. The medication was completed by reducing the dose in a month. Patients in the systemic steroid group were advised to receive the medication after eating, to restrict salt and sugar consumption throughout the treatment, to quit smoking if they are using, and a proton pump inhibitor was started.

Group L: Triamcinolone acetonide (40 mg TCA: Kenacort ampul; Deva Holding, Istanbul, Turkey) was administered to the patients through injecting inside the lesion. The practice was based on the dose of TCA administered in acute and chronic inflammatory skin lesions. If the lesion is single-focused and small (<5.0 cm), 20mg/mL TCA was injected and if the lesion is multifocal or large (>5.0 cm) then 40mg /mL TCA was injected into the lesion with the guidance of ultrasonography [11,12].

Steroids were diluted with saline physiological and adrenaline-free lidocaine before the administration. The procedure for multifocal lesions was repeated at intervals of one week, not exceeding the dose of 40 mg/ml TCA at a time. This sentence will be corrected this way. The total dose administered to the patients was between 40 mg and 200 mg TCA. The process is shown in video 1.

Assessment of Response to Treatments

All patients were screened through ultrasonography (USG) before the treatment. Also, magnetic resonance imaging (MRI) was performed in some cases. All patients were assessed by physical examination one week after the treatment was completed. Afterward, follow-up for the patients was performed through physical and radiological examination (USG, MRI) at the 1st, 3rd, and 6th months.

Reduction in the manifestations of inflammation such as fever, redness, abscess, levels of C-reactive protein (CRP), retraction and disappearance of edema in the breast skin, recuperation of ulcers and fistulas, the disappearance of the palpable masses were determined as complete clinical regression (CCR).

Radiological analysis was performed by measuring the size of the lesion before and after the treatment. Regression of the lesion less than 50% was considered as incomplete radiological regression (IRR) whereas 50-75% regression was identified as partial radiological regression (PRR). Meanwhile, regression with a rate of 75-99% was categorized as advanced radiological regression (ARR), and disappearance of radiological findings were labeled as complete radiological regression (CRR). Regression in the sizes of lesions at a rate of 75% and more were interpreted as a radiological response to the treatment (RRT). Patients who responded to the treatment both clinically and radiologically (CCR, RRT) were considered to be responsive to the treatment (RT).

Patients who had had progress in clinical and radiological findings throughout the treatment, who had no regression in lesions that are anticipated to remain stable (<75%), or had a recurrence of the disease after 6th months was interpreted as being unresponsive to the treatment (URT), while patients who did not participate to follow-up regularly, who experienced a loss of follow-up, or who gave up the treatment due to adverse effects were identified as treatment incompatibility (TIC).

Treatment Endpoints

CCR or URT during the treatment were the endpoints of the treatment, in all groups. The occurrence of systemic adverse effects in the course of the treatment was considered as the reason to discontinue the medication in all groups. The duration of systemic steroid treatment was planned as one and a half months, based on our daily practice. However, arrangements were made according to the severity of the disease. The follow-up period ended in 6 months after the treatment was completed.

Data

Patients demographics, duration of disease, physical examination findings, imaging, microbiological results and pathology records were recorded prospectively.

Statistical Analysis

The software program of SPSS version 15 for Windows (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis of the data. To compare the distribution of frequencies in variables among groups, the Chi-square test or Fisher's exact test was used. Statistical significance was considered as $p<0.05$.

Results

36 female patients with a mean age of 35.4 ± 6.7 years were included in the research. None of the patients had a previous history of undergoing treatment for granulomatous mastitis.

The systemic steroid group comprised of 19 patients, while the local steroid group comprised of 17 patients. All patients received antibiotic medication before the diagnosis while waiting for a biopsy result (minimum 7 days and maximum 21 days peroral). All patients had a painful mass in the breast during admission, while of the patients, 16 (44.4%) had an abscess, 4 (11.1%) had a fistula in the breasts, and 1 (2.8%) had ulcers. The two groups were analogous in terms of the size of the lesions detected through USG and MRI. The demo-

TABLE I - *The demographic characteristics and clinical findings of the patients.*

		All patients (n. 36)	Group S (n. 19)	Group L (n. 17)
Age (n/%)				
	<35	16 /44.4	9 /47.3	7 /41.2
	35-45	15 /41.6	7 /36.8	8 /47.1
	>45	5 /14	3 /15.9	2 /11.7
TAC (n/%)				
	<5 year	19 /52.8	10 /52.6	9 /52.9
	≥5 year	17 /47.2	9 /47.4	8 /47.1
	nullipar	0 /0	0 /0	0 /0
TAB (n/%)				
	<5 year	26 /72.2	13 /68.4	13 /76.5
	≥5 year	10 /27.8	6 /31.6	4 /23.5
	nullipar	0 /0	0 /0	0 /0
	No breastfeed	0 /0	0 /0	0 /0
Menopausal statement (n/%)				
	postmenopausal	1 /2.8	1 /5.3	0 /0
	premenopausal	35 /97.2	18 /94.7	17 /100
Use of antibiotic (n/%)		36 /100	19 /100	17 /100
	-time, week (median/range)	1.8 (1-4 week)	1.3 (1-3 week)	2.4 (1-4 week)
Pattern of the disease (n/%)				
	unilateral	36 /100	19 /100	17 /100
	bilateral	0 /0	0 /0	0 /0
Unifocal (n/%)		17 /47.2	11 /57.9	6 /35.3
Multifocal (n/%)		19 /52.8	8 /42.1	11 /64.7
Presence of fistula (n/%)		4 /11.1	1 /5.3	3 /17.6
	single	3 /8.3	1 /5.3	2 /11.7
	multiple	1 /2.8	0 /0	1 /5.9
Presence of lump (n/%)		36 /100	19 /100	17 /100
Presence of ulcer (n/%)		1 /2.8	0 /0	1 /5.9
Presence of abscess (n/%)		16 /44.4	8 /42.1	8 /47.1

Group S: systemic-peroral steroid group; Group L: local-intralesional steroid group; TAC: time after childbirth; TAB: time after breastfeeding

graphic characteristics and clinical findings of the patients are presented in (Table I).

Of the local steroid group, 13 patients received single, and 4 patients received multiple injections. Patients requiring multiple injections had 3 or more lesions. The medication was repeated in five patients of the systemic steroid group in whom no regression was observed during the 1st-month control.

Of the patients in the systemic steroid group; 10 patients (52.6%) at the 1st month, 17 (89.5%) at 3rd month, and similarly 17 (89.5%) at the 6th month responded clinically to the treatment. Moreover, of the patients in this group, 8 patients (42.1%) at the 1st month, 15 (78.9%) at the 3rd month, and similarly 15 (78.9%) at the 6th month responded radiologically to the treatment. At the end of the 6th month the RT rate was calculated as 78.9%. Clinical findings also disappeared in all patients who responded radiologically to the treatment. In terms of treatment response, there was no difference between the 3rd and 6th months. 4 patients in the group did not respond to treatment at the end of the 6th month. Three of the patients who did not respond to the treatment were multifocal.

In the local steroid group; 10 (58.8%) patients in the 1st month, 15 (88.2%) in the 3rd month, and 15 (88.2%) in the 6th month were found to have clinical responses. Meanwhile, the radiological response was detected in 9 patients (52.9%) in the 1st month, in 15 patients (88.2%) of 3rd month, and this rate did not change in the 6th month. The rate of RT was calculated as 88.2% at the end of the 6th month. Only two of 17 patients treated with local steroids were considered unresponsive to the treatment at the end of the 6th month. Both of the patients had multi-focal lesions.

Treatment incompatibility was not determined in any patient. Two patients in the oral steroid group complained of gaining weight (less than 5% of their weight). In one of the patients who underwent local administration, hyperemia of the skin developed after the first administration. It was found in the examination of the patient one week later that the hyperemia had disappeared. Hyperemia and thinning skin were observed in another patient in the 2nd month after injection, and local treatment was performed on the patient with cicatrizant drugs. Clinical and radiological responses and recurrence rates of patients at the 1st month, 3rd month and 6th month are presented in (Table II).

Control examinations on the 3rd month were determinative for all patients in response to the treatment. The response remained unchanged on the 6th month, but

TABLE II - *Clinical and radiological responses and recurrence rates of patients at the 1st month, 3rd month and 6th month.*

		All patients (n:36)	Group S (n:19)	Group L (n:17)	p value
1st month					
CCR (n/%)		20/55.6	10/52.6	10/58.8	p=0.709
Radiological response (n/%)					
	CRR	1/2.8	1/5.3	0 /0	p=0.953
	ARR	16/44.4	7/36.8	9 /52.9	
	PRR	7/19.4	5/26.3	2 /11.8	
	IRR	12/33.3	6/31.6	6 /35.3	
3rd month					
CCR (n/%)		32/88.9	17/89.5	15/88.2	p=0.655
Radiological response (n/%)					
	CRR	17/47.2	12/63.2	5 /29.4	p=0.657
	ARR	13/36.1	3/15.8	10 /58.8	
	PRR	2/5.6	1/5.3	1 /5.9	
	IRR	4/11.1	3/15.8	1 /5.9	
6th month					
CCR (n/%)		32/88.9	17/89.5	15/88.2	p=0.655
Radiological response (n/%)					
	CRR	23/63.9	12/63.2	11 /64.7	p=0.567
	ARR	7/19.4	3/15.8	4 /23.5	
	PRR	5/13.9	3/15.8	2 /11.8	
	IRR	1/2.8	1/5.3	0 /0	
Responsive to the treatment	30/83.3	15/78.9	15/88.2	p=0.662	
Unresponsive to treatment	6/16.7	4/21.1	2/11.8	p=0.662	
Treatment incompatibility	0/0	0/0	0/0		
Side effect	4/11.1	2/10.5	2/11.8	p=1	
Treatment repetition	9/25	5/26.3	4/23.5	p=1	

CCR: complete clinical regression, CRR: complete radiological regression, ARR: advanced radiological regression, PRR: partial radiological regression, IRR: incomplete radiological regression.

the lesion's regression must be written. was slightly increased, albeit inadequate. It was found out that there was no statistically significant difference between the two groups in terms of treatment efficacy, adverse effects, and convalescence rates. However, it was found out that the recovery rate of the patients in the group, which had been administered locally, outnumbered the other group, and one of the patients who did not benefit from the systemic treatment showed recuperation thanks to the local administration. None of our patients give up their treatment. An example of response to local treatment is shown in (Fig. 1).

Discussion

IGM is an illness that has not had a clear consensus about its treatment since the day it was identified. The most frequently practiced treatments are surgical excision of granuloma, abscess drainage, and concomitant steroid medication [5]. In the literature, steroids have been used as a primary therapy or as a conservative treatment to reduce the size of non-resectable lesions prior to surgery. Steroids are also administered after the excision in resistant and complicated cases to prevent the potential recurrence of IGM [13].

Adverse effects and the recurrence rates of medical treatment as well as the inadequate cosmetic results of surgical treatment led to an ongoing quest for optimum treatment [14].

In our study we compared systemic application of steroids with intralesional application which provides shorter treatment time and shows fewer side effect and we concluded that intralesional administration of steroids are as effective as systemic administration in the treatment of IGM.

In the studies done for IGM, the treatments involved systemic steroids, topical steroids or surgical interventions. These treatment options were compared in terms of efficacy and recurrence rate. In the literature, the recurrence rate following systemic steroid applications was reported as 16-50% depending on the follow-up time [15,16].

In a study conducted by Marzieh Salehi et al.in 2014, 39 patients were treated with surgical treatment, while 20 patients were cured with the medication of azithromycin and prednisolone. It was put forward in this research that there was no significant difference between the surgical and medical treatment regarding the recurrence rate of IGM [13].

In their study, Mızraklı et al. suggested that steroid was proper and effective treatment for IGM, upon perform-

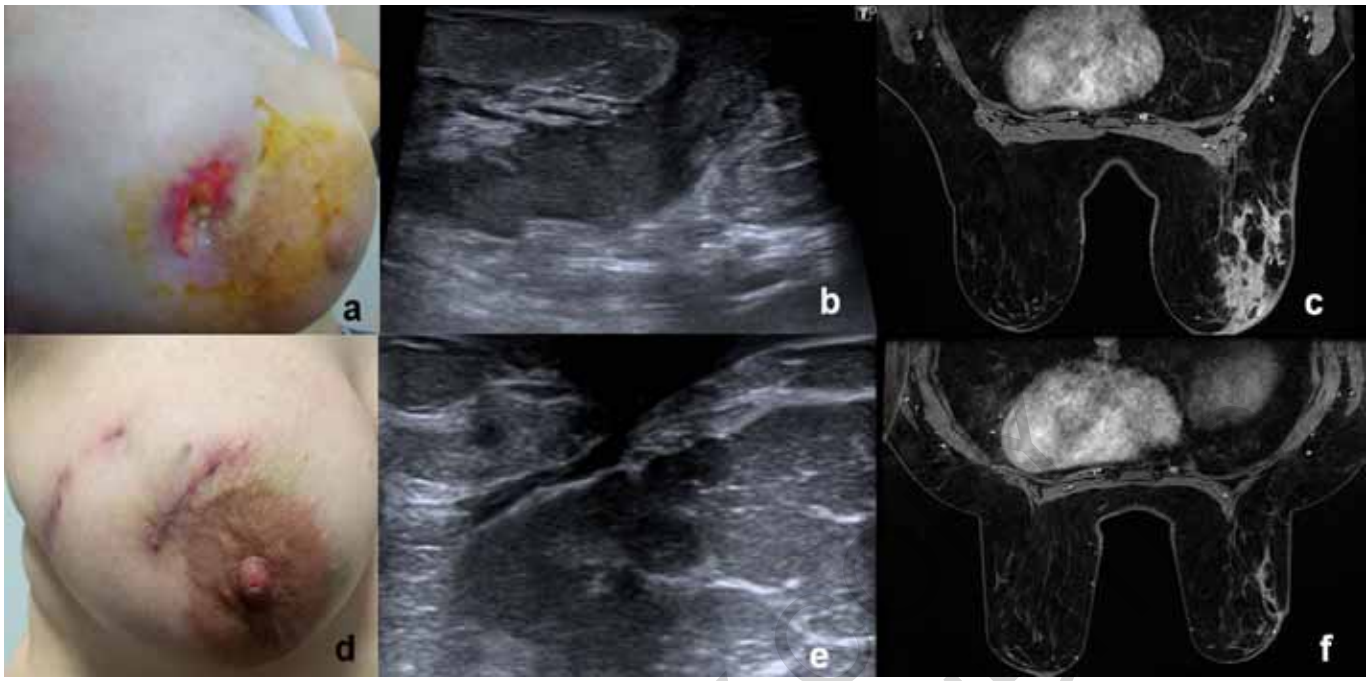

Fig. 1: A 32-year-old female patient who previously had abscess drainage due to granulomatous mastitis admitted to us with a complaint of discharge from the incision line in the right upper quadrant.
A) At the USG examination, the collection area that opened to the skin at the level of the incision was observed; B) Axial contrast-enhanced T1-weighted sequence revealed increased contrast enhancement at inflamed area that extending into deep planes the upper outer quadrant of right breast; C) at the end of five times of intralesional steroid injection during six months, it was observed in the clinical examination that the fistula mouth was closed and the inflamed appearance was regressed; D) at the USG examination; E) and contrast-enhanced T1-weighted sequence; F) the regression of the inflammation was significant.

Video 1 - Adminstiration of intralesional steroid injection.

ing steroid therapy to 40 of the 49 patients who had IGM [17].
In addition to that, in a series consisting of 40 patients, Atak et al. administered NSAID, antibiotics, steroids, and performed drainage and surgical excision to the patients. In this series, it was determined that the total recurrence rate was 37%, while it was 16% in oral steroid treatment and 14% after surgical excision [18].
Meanwhile, it was revealed in other studies that steroids lead to the regression of the lesion and long-termed medication with steroids ends up with a complete recovery [19].
In a series of 28 patients who underwent intralesional steroid application, the full response rate was 89.3%. The recurrence rate was reported as 10.7% [20].
Considering the above-mentioned researches, it could be stated that the steroid medication is the most preferred practice for the treatment of IGM, and it indicates similar results with the surgery. However, given the systemic adverse effects of steroid therapy, the search for a treatment that could cause fewer side effects. Intralesional steroid injection can also be considered to be one of the methods that might be suitable for the treatment.
In our study, response to the treatment rate of the group which had been given systemic steroid was similar with the literature. In the group which had been given steroid locally, although the treatment response was higher, there was not any statistically significant between 2 groups both clinically and radiologically.
Intralesional steroid administration was more successful than in single-focal lesions, and achievement was attained in multi-focal doses when the dose was administered in several sessions with one-week intervals.
No significant adverse effects occurred during the treatment in both groups.

Conclusion

As a consequence, it can be stated that the local (intralesional) steroid administration is also a treatment method, which is comparable to systemic steroid administration also had similar side effects. This study has two main limitations. The first limitation is the small number of patients, and the second is the short follow-up period, which may affect the recurrence rate data. Nevertheless considering the low incidence of IGM in the general

population, our patient number still cannot be underestimated. Further studies with higher number of patients are needed to support our findings regarding the efficacy of intralesional steroid applications in IGM.

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Riassunto

La mastite granulomatosa idiopatica che non ha avuto un chiaro consenso circa il suo trattamento dal giorno in cui è stata identificata, è una rara malattia infiammatoria benigna della mammella, che imita la malignità per le sue caratteristiche del suo aspetto.
Nella nostra ricerca, intendevamo confrontare l'efficienza della somministrazione intralesionale e sistemica di steroidi nel trattamento della mastite granulomatosa idiopatica con uno studio prospettico randomizzato e controllato.
Sono state incluse nello studio un totale di 36 donne a cui era stata diagnosticata su base istopatologica una mastite granulomatosa idiopatica, con esclusione di altri fattori microbiologici.
Le pazienti sono state randomizzate in due sottogruppi da trattare con steroidi sistemici oppure intralesionali. Tutte le pazienti sono state valutate tramite esame fisico una settimana dopo il completamento del trattamento. Successivamente è stato eseguito il follow-up delle pazienti con un esame fisico approfondito, ecografia e/o la risonanza magnetica al 1°, 3° e 6° mese.
RISULTATI: tutte le pazienti si sono adattate al trattamento. La regressione clinica completa si è verificata in 32 pazienti, mentre 30 dei 36 pazienti hanno risposto al trattamento sia radiologicamente che clinicamente. 4 pazienti hanno avuto effetti collaterali minori. È stato constatato che non vi era alcuna differenza statisticamente significativa tra il gruppo delle trattate con steroidi locali e quelle con trattamento sistemico in termini di regressione clinica completa, risposta agli effetti collaterali del trattamento e tassi di recidiva.
CONCLUSIONE: anche la somministrazione intralesionale di steroidi è stata considerata un metodo di trattamento efficace come la somministrazione sistemica di steroidi.

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