Conservative management of 154 patients with idiopathic granulomatous mastitis: Simple is better?

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PURPOSE: *Both the aetiology and treatment of idiopathic granulomatous mastitis (IGM) is controversial and unnecessary resections can lead to over-treatment in such a benign disease. Our aim was to report our experience in patients with IGM managed mainly with conservative methods, such as antibiotics, drainages and corticosteroids.*
MATERIAL AND METHODS: *Pathology database from 2008 to 2018 was reviewed retrospectively. Demographics and symptoms were documented from patient charts. Follow-up information was obtained from clinical reviews, and severity and duration of symptoms were documented. All data were transferred to Excel file and the parameters were compared.*
RESULTS: *All 154 patients were women. Mean age was 35.9 years. Empiric broad-spectrum antibiotic, abscess drainage and steroid treatments were seen to be successful in most of the cases (95.4%). In patients with limited regression (2.5%) or persistant lesions (1.9%), a second cycle was employed with a total regression rate of 100%. Recurrence was seen one or two times in 23 (14.9%) and 2 (1.2%) patients in a mean follow-up period of 5.3 years. The average time of recurrence was 2.5 years (range, 9-74 months).*
CONCLUSIONS: *Conservative management could be efficacious for IGM, and less and simpler can be enough to achieve more effective results.*

KEY WORDS: Abscess drainage, Antibiotics Idiopathic granulomatous mastitis (IGM), Conservative management, Corticosteroids

Introduction

Idiopathic granulomatous mastitis (IGM) is a chronic nonspesific inflammation of the breast, and its diagnosis can be made by the exclusion of other granuloma-forming diseases or specific infections, such as tuberculosis and sarcoidosis [1-3]. It is usually known as a benign and self-limiting disorder, and affects most commonly young or middle-aged parous women. However, its differential diagnosis from specific mastitis or breast cancer should be done, as it may present as a firm solitary mass associated with an inflammatory skin fistula or an abscess. Imaging scans can be helpful, but biopsy is the only choice in establishing the definitive diagnosis [4].
The management of IGM is also controversial, and treatment options include antibiotics, abscess drainage, corticosteroids, wide resections, quadranectomy and even simple mastectomy [5-7]. Immunosuppressive agents such as methotrexate and azathioprine have also been implicated in the treatment of IGM, even their use can be debatable especially in women of child-bearing age [8,9]. The English-written literature of our Pub-Med search has revealed that most of the studies are case reports or retrospective case series with small numbers of patients, and from the time of when the disease was first described

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in 1972, great majority of trials have announced the results of repeated incisions or wide local excisions to obtain disease-free margins before or after steroid use [10-12]. However, the cosmetic results of the surgery are very poor and systemic corticosteroids are still employed to prevent recurrences. There are also some reports on low or high dose steroid treatment in IGM, with moderate or high resolution rates, but most of these studies are concerned about the well-known side effects of these medications [13,14].

Since the breast abscess seen in IGM is usually sterile, many studies in the literature do not recommend the use of antibiotherapy [5,15]. As glucocorticoids cause immunosuppression to some extent, it may not be safe to start them in the presence of a bacterial infection. However, the risk of secondary infection is underestimated in these trials with limited number of patients.

The purpose of this study is to report our experience in IGM patients who were managed mainly with conservative methods, such as broad-spectrum antibiotics, simple drainages and oral corticosteroids. In the current series with 154 patients, we first started treatment with simpler measures, taking account of their needs at that moment. Then, the management was further oriented according to their response, in parallel with the notion that unnecessary resections can lead to over-treatment in such a benign, self-limiting, recurrent disease.

Material and Methods

The study was approved by our institution's Ethics' Committe (SBU /21.11.2018/B.10.1.TKH.4.34.H. GP. 0.01/137). We retrospectively reviewed a pathology database from 2008 to 2018, covering the last 10-year period. Demographics and symptoms were documented retrospectively from the HIS (Health Information System) and all data were transferred to the Excel file (Office 2007, Microsoft, U.S.).

In patients with suspected IGM, ultrasound (US) was carried out on all, and mammography (MMG) was obtained from the ones ≥ 40 years. Magnetic resonance (MR) scan was also used for the differential diagnosis in complicated cases. Hypoechoic, lobulated, irregular mass, and/or ill-defined increased radio-opacity with some spiculations, or heterogenous mass causing parenchymal distortion were detected in these scans, respectively (Fig. 1).

The diagnosis was confirmed by either core needle biopsy (CNB) or also from biopsy specimens taken from the abscess wall during drainage. Breast tru-cut biopsy specimens were fixed in 10 % neutral-buffered formalin and 5-micrometer sections were stained using Hematoxylin and Eosin (H&E) dye. All slides were examined by an experienced pathologist. Histopathological examination of the core biopsies revealed loose collections of macrophages admixed with Langhan's multinucleate giant cells surrounded by lympho-plasmacytic infiltrate around ductules and lobules, which is called granulomatous inflammation (Fig. 2). These were non-caseating granulomas. There was also suppurative inflammation found in the backround. Specific stains, such as Gram, Ziehl-Neelsen, Grocott and periodic acid–Schiff, were used to exclude the presence of any micro-organisms. Patients with IGM were included in the study, when all other possible causes of granuloma formation were excluded.

All abscesses ≥2 cm were drained. In all patients with infectious and/or inflammatory signs or with abscesses, a broad spectrum empiric antibiotic was employed for

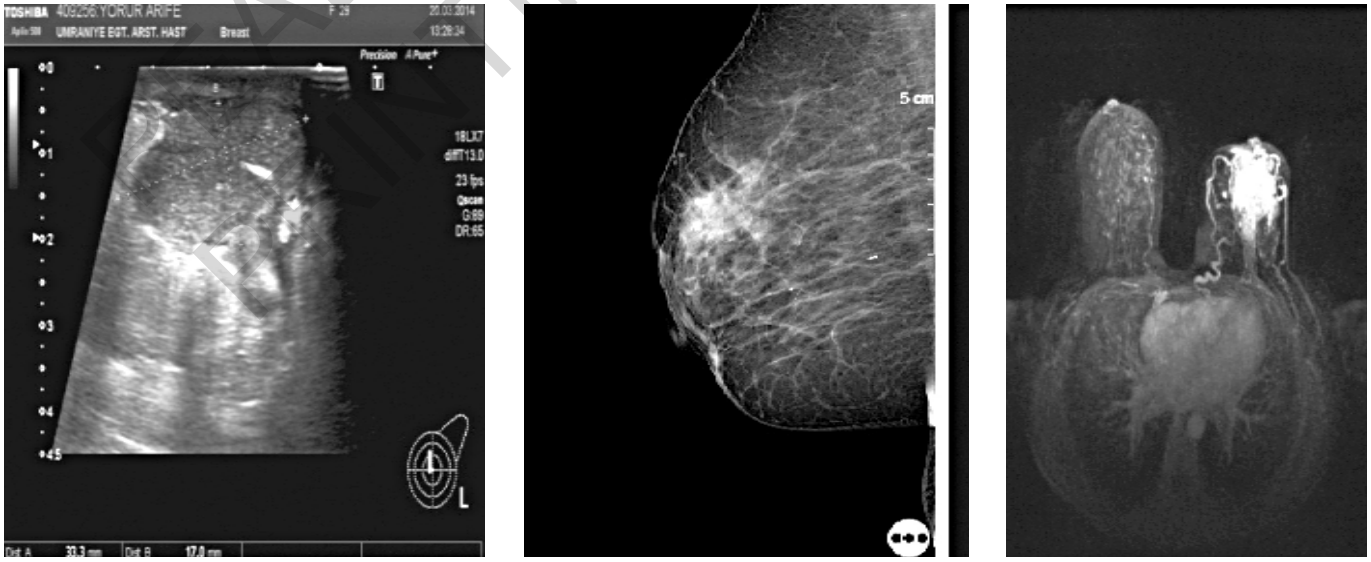

Fig. 1: Radiological findings of IGM: Hypoechoic, lobulated, irregular mass (US), ill-defined increased radio-opacity with some spiculations (MMG) and heterogenous mass causing parenchymal distortion (MR).

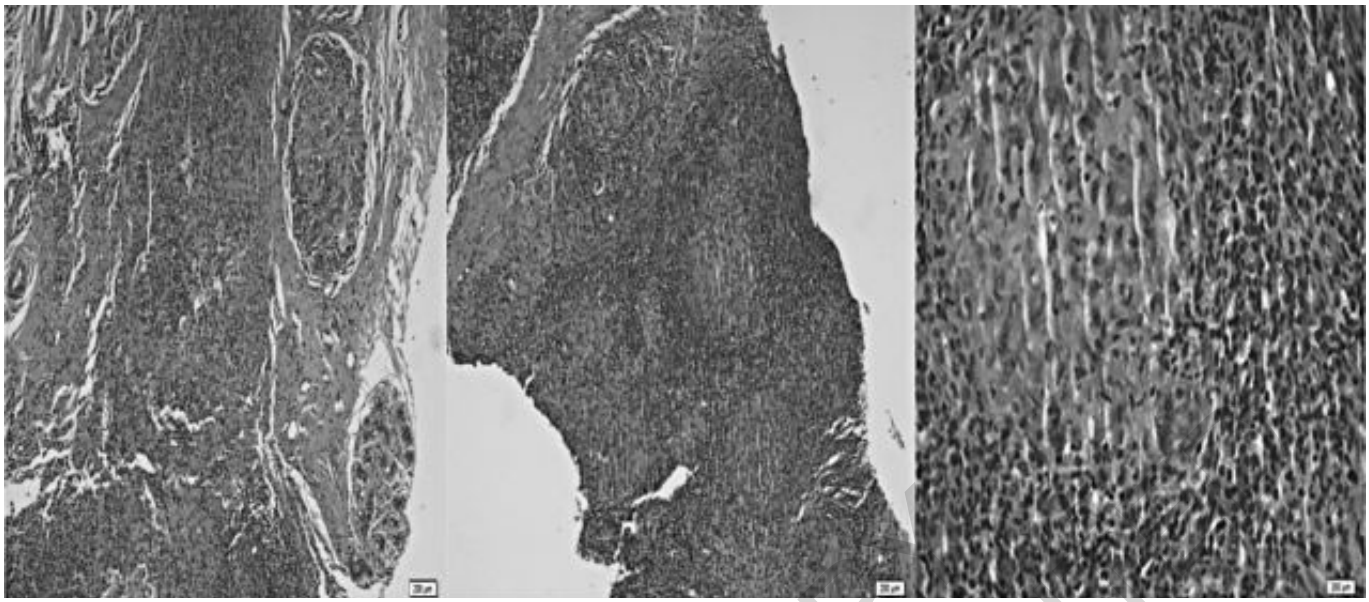

Fig. 2: Supurative granulomatous inflammation around ducts and lobules (x10), non-caseating granulomas (x10) and Langhan's type giant cell (x40).

at least 10 days. In few patients presenting with masses as the primary complaint, without any sign of infection or abscess (n=19, 12.3%), biopsy results were waited for. Following the definitive diagnosis of IGM was obtained, all used prednisolone (Mustafa Nevzat Ilac San AS, Istanbul) treatment with the same high-dose as 64 mg/day for the first four weeks, and then the corticosteroid dose was tapered in the following 2 weeks. In recurrent cases, the same treatment cycle was used one more time. We did not use local steroid cream or pomads in any cases, but St. John's wort (hypericum perforatum) oil massage (two times daily, for two minutes) was recommended to our last 10 patients with recurrent diseases, following steroid usage.

Follow-up information was obtained from clinical reviews, and type, severity, and duration of the symptoms were documented. Patients without follow-up were excluded from the study. The data were transferred to the same Excel file and then, the parameters were compared retrospectively.

TABLE I - *Symptoms/clinical signs*

Symptoms	N	%
Hyperemia/erythema/cellulitis	135	87.6
Mass	116	75.3
Abscess*	57	37
Fistula formation	23	14.9
Ulceration	11	7.1
Nipple retraction	6	3.8
Axillary lymphadenopathy	5	3.2
Peau d'orange sign	2	1.2

*Number of abscesses <2 cm was 14

Results

All 154 patients were women. Mean age was 35.9 years (range, 16-71). While the numbers of patients ≥45 and ≤18 year-old were 19 and 2, respectively (12.3% and 1.2%), their mean ages were estimated to be 54.8 and 17 years. Most of the patients (n=133, 86.3%) were in the reproductive age (mean, 34.4 years). Seven patients (4.5%) were nulliparous, 2 patients (1.2%) were in their first pregnancy (1.2%), and all others (n=145, 94.1%) had at least 3 children (range, 1-7). Twenty per cent of the patients had a history of oral contraceptive use (n=31), and another 18 patients were using anti-depressant medications (11.6%). Twelve patients had controlled diabetes mellitus and twenty-one had a smoking history (7.7% and 13.6%, respectively). There was no endocrinologic or autoimmune diseases, except thyroid disorders in 16 patients (10.3%). US (n=154), mammography (n=36) and MR (n=14) were used in 100%, 23.3% and 9% of the patients, respectively. Clinical presentation was seen to be in a wide range from simple hyperemia/erythema to gross mass or masses (Fig. 3). Physical examination revealed mostly cellulitis (n=135, 87.6%) and breast mass (n=116, 75.3%) (Table I). The average diameter of masses on US scan was 34 mm (range, 18-96). Most of the lesions were located in the upper outer quadrants (n=66, 40.5%, Table II). In six patients, lesions were seen in both right and left breasts (3.8%). Empiric broad-spectrum antibiotic, abscess drainage and steroid treatments were seen to be successful in most of the cases (n=147, 95.4%, Table III). In these patients, the lesions regressed significantly or disappeared totally in a mean of 6 weeks (range, 1-10) (Fig. IV). In patients with limited regression (n=4, 2.5%) or persistant lesions

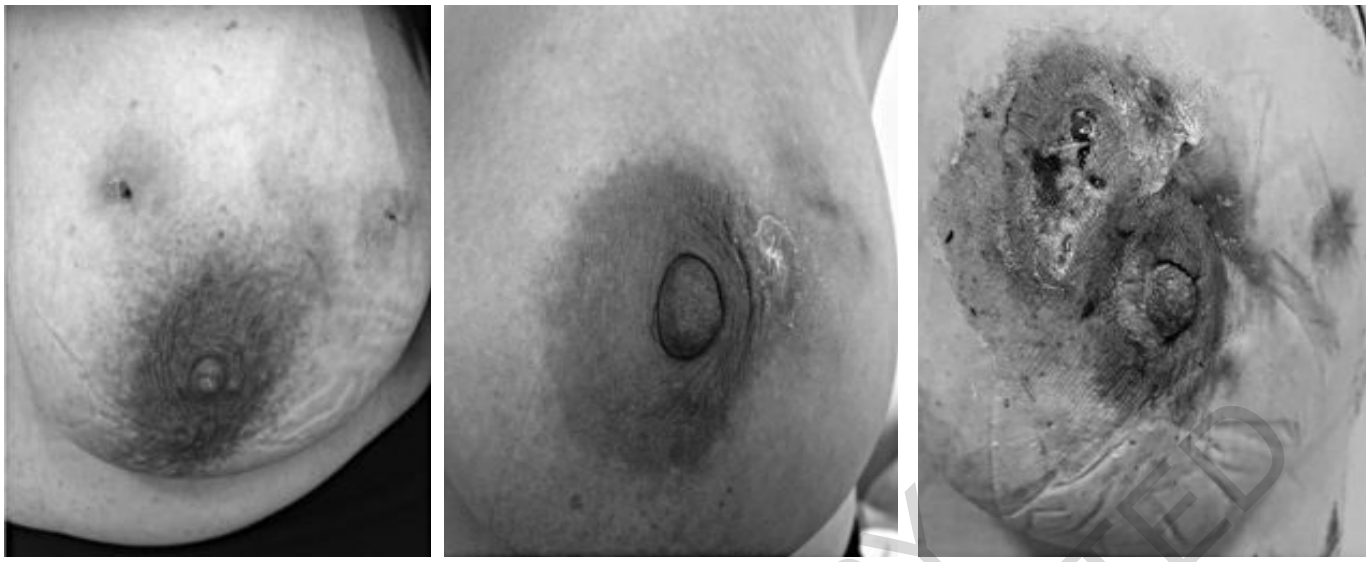

Fig. 3: Clinical presentation of IGM, before treatment.

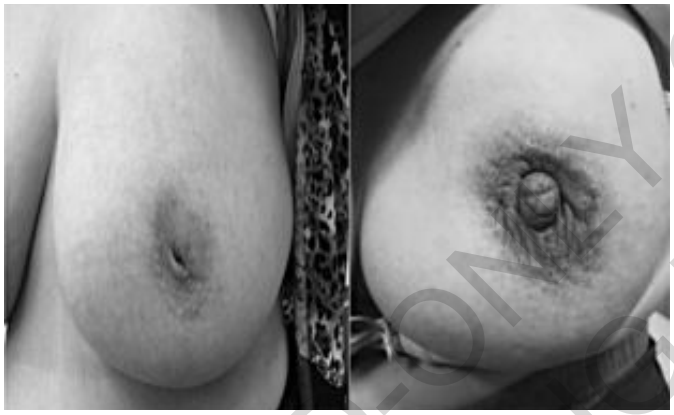

Fig. 4: Clinical presentation of IGM, after treatment.

(n=3, 1.9%) after the first steroid cycle, a second cycle was started following a 4-week interval (n=7, 4.5%), and one patient required a second drainage before streoid treatment (0.6%). The outcome was outstanding in these patients, as well, with a total regression rate of 100% (n=7). Pregnant patients were treated only with abscess drainage, and they responded well. Even though the results were successful, recurrence was seen one or two times in 23 and 2 patients, respectively (14.9% and 1.2%), in a mean follow-up period of 5.3 years (range, 10-129 months). The average time of recurrence was estimated as 2.5 years (range, 9-74 months). None of the patients had disease progression, and no surgical intervention was required except drainage. We did not see any complication of the steroid treatment.

Discussion

IGM is a rare, benign and chronic inflammatory granulomatous disease with unknown origin that typically affects women of child-bearing age [1,2]. It usually presents with a tender breast mass and is often associated with an abscess or inflammation of the overlying skin. Nipple inversion, peau d'orange sign, ulcerations and

TABLE II - *Localization of the lesions*

Localization*	**Left (n=90, %)**	**Right (n=70, %)**	**Total (n=160, %)**
Upper outer quadrant	37 (40.2%)	29 (40.8%)	66 (40.5%)
Upper inner quadrant	20 (21.7%)	16 (22.5%)	36 (22.1%)
Lower outer quadrant	14 (15.2%)	13 (18.3%)	27 (16.6%)
Lower inner quadrant	21 (22.8%)	13 (18.3%)	34 (20.8%)
Multifocality	3 (3.6%)	2 (3.1%)	5 (3.3%)
Multicentricity	2 (2.3%)	1 (1.5%)	3 (2%)
Bilateral involvement**	6 (3.8%)		

*84 patients had left, 64 patients had right, and 6 patients had bilateral breast involvement, **There was no multicentricity in patients with bilateral involvement

TABLE III - *Treatment modalities and response rates*

Treatment	Patients (n, %)	Response rate (n,%)
Broad-spectrum antibiotics	133 (86.3%)	130 (97.7%)
Abscess drainage*	43 (27.9%)	42 (97.6%)
Steroids	152 (98.7%)	148 (97.3%)

*All abscesses ≥2cm was drained (n=43), while smaller abscesses (<2cm) were started on empiric antibiotics

fistula formation can occur as a result of disease progession, and IGM can easily be mistaken for breast carcinoma [3]. Since its clinical and radiological findings are nonspecific, a core biopsy is mandatory to exclude both the other granuloma-forming inflammatory diseases and the carcinoma. Current literature has described an association with contraceptive pills, lactation, antidepressant drug usage causing hyperprolactinemia and smoking [16,17]. Autoimmune background of the patients with IGM has also been interrogated [1,13]. Although most of our findings are consistent with the literature in general, a high rate of women older than 45 years (12.5%) and nulliparous women (4.5%) and the lower incidence of smoking (13%), oral contraceptive (20%) or antidepressant (11%) usage and autoimmune history (10%) in our series suggest that this disease can be encountered in a wide spectrum of women independent of certain risk factors. In our opinion, establishing an assertive relationship between these factors and IGM described in aforementioned studies may be related to low number of patients evaluated.

There is no general consensus in the literature on management of IGM and optimal treatment has not been yet established. Most surgeons have limited experience in managing this clinical entity, and the disease has a high recurrence rate, variously reported between 16% and 50% [18,19]. From the time of when the disease was first described in 1972, most of the studies have prioritized surgery, and some of them have reported the results of repeated incisions or wide local excisions to obtain disease-free margins [5,10]. Later on, corticosteroids and even some immunosuppresive agents, such as methotrexate and azathioprine, have been used to prevent recurrences or to limit the extent of surgery [8,9]. However, the overall results are frustrating since the cosmetic outcomes of surgery is unacceptable and the recurrence rates are still very high. In our opinion, even some good results in limited number of patients with short outcomes have been reported, the use of immunosupressive drugs in such a self-limiting, benign disease and in women of child-bearing age should be interrogated, especially if they were employed for steroid dosage tapering. Wilson et al. [20] have reported only a partial response to low-dose oral corticosteroids as primary therapy (58%), and they have performed complete excision, including partial and simple mastectomy. However, recurrence rate in their series is still high (21%). In another study published in 2017, the treatment modalities for IGM have been reported as antibiotics (57%), corticosteroids (21%), methotrexate (7%), and/or surgery (71%) [21]. There are also recent trials recommending surgical excisions after steroid treatment or vice versa [22,23].

There are also some studies interrogating the role of antibiotics in IGM [5,15]. Since the breast abscess seen in IGM is usually sterile, they do not recommend the use of antibiotherapy. However, the risk of secondary infection is underestimated in these trials with limited number of patients. There are also current publications reporting that treatment with high dosages of oral prednisone, alone or in combination with surgery, is effective [19]. Sakurai et al. [24] reported a series of 8 patients with IGM, and treated 7 of the 8 patients with only corticosteroids. The authors obtained a complete remission in 5 to 10 months. However, in other reports, weight gain, hyperglycemia, oral candidiasis and gastritis were reported as side effects of corticosteroid treatment [25]. On the other hand, some current reports recommend just observation and close follow-up when IGM diagnosis is obtained [26]. In these studies, operations are limited to drainage procedures for fluid collections and no medications are prescribed. This approach may seem to be logical since IGM is a self-limited, benign condition that waxes and wanes, and eventually resolves. However, in our opinion, leaving the patient without treatment especially in the presence of intractable symptoms is unacceptable both medicolegally and humanly.

Considering all previous studies and above-mentioned facts made us think that the management of IGM cases needs to be tailored according to the clinical presentations. In the current series with 154 patients, we first started treatment with simpler measures, taking account of their needs at that moment. Then, the management was further oriented according to their response, in parallel with the notion that unnecessary resections can lead to over-treatment in such a benign, self-limiting, recurrent disease. In our series, we felt free to use antibiotics for at least 10 days to resolve the most common symptoms, hyperemia/erythema/cellulitis (87%), and drained all abscesses ≥2cm, as well. This treatment modality itself was very successful (97%), and let us save time till the definitive diagnosis was obtained as IGM. Since the most effective weapon we have, to subside the acute flares and to prevent recurrences, is the corticosteroids, we preferred to use them in high doses for 4 weeks with a gradual tapering in the following 2 weeks. In our 147 patients, the lesions regressed significantly or disappeared totally in 6 weeks (95%). However, in cases with limited regression or persistent symptoms (4.5%), a second cycle of treatment was started after a 4-week interval. All patients responded well. Moreover, the recurrence rate in the current series was very low (15% of patients had one and 1% had two episodes). We did not see any steroid-related complication, as well.

Conclusion

The present study has shown that conservative manegement with simple drainages, antibiotics and hight dose corticosteroid therapy could be efficacious for IGM. To our knowledge and experience, management of IGM patients needs to be tailored according to the clinical presentations, and less and simpler approach can be enough to achieve more effective results. The management should be oriented according to the notion that unnecessary resections can lead to over-treatment in such a benign, self-limiting, recurrent disease.

Riassunto

Sia l'eziologia che il trattamento della mastite granulomatosa idiopatica (IGM) sono controversi e resezioni non necessarie possono portare a un trattamento eccessivo in una malattia così benigna. Il nostro obiettivo è quello di riferire la nostra esperienza di gestione di pazienti con IGM principalmente con metodi conservativi, come antibiotici, drenaggi e corticosteroidi.
È stato studiato retrospettivamente il nostro registro anatomo-patoliogico dal 2008 al 2018 rilevando dati demografici e sintomatologia dalla documentazione dei grafici dei pazienti. Le informazioni di follow-up sono state ottenute da revisioni cliniche e sono state documentate la gravità e la durata dei sintomi. Tutti i dati sono stati trasferiti in file Excel e i parametri sono stati confrontati.
Tutti i 154 pazienti erano donne. L'età media era di 35,9 anni. Nella maggior parte dei casi, l'antibiotico ad ampio spettro è stato scelto empiricamente, il drenaggio dell'ascesso e i trattamenti con steroidi sono risultati efficaci nel 95,4% dei casi. Nei pazienti con regressione limitata (2,5%) o lesioni persistenti (1,9%), è stato impiegato un secondo ciclo con un tasso di regressione totale del 100%. La recidiva è stata osservata una o due volte in 23 (14,9%) e 2 (1,2%) pazienti in un periodo di follow-up medio di 5,3 anni. Il tempo medio di ricorrenza è stato di 2,5 anni (intervallo, 9-74 mesi). Si conclude che la gestione conservativa potrebbe essere efficace per IGM e un trattamento meno invasivo e più semplice può essere sufficiente per ottenere risultati efficaci.

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