Original Article

Methylprednisolone for idiopathic granulomatous mastitis: a prospective observational cohort study

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Background: Idiopathic granulomatous mastitis (IGM) is a rare, benign, but locally aggressive breast disease. Steroids are widely used as a breast-conserving option, however, the response rate of steroids varies in reported studies, as well as its different reported usage. This prospective observational cohort study aimed to report the outcomes of methylprednisolone for IGM treatment.

Methods: From Aug 2019 to Dec 2021, the clinicopathological information of 156 IGM patients who sought treatment at West China Hospital was prospectively collected. A total of 88 patients treated with methylprednisolone were included in the study. The clinical features, treatment response, and follow-up data were analyzed.

Results: The median age at diagnosis was 32 years, and 90.9% of patients were multipara. The predominant symptom at presentation was painful breast mass, with a median size of 4.7 cm. For steroid usage, an initial 20 mg methylprednisolone daily was given until disease stable. The median duration of 20 mg methylprednisolone treatment was 45 (range, 14–376) days. The median duration of whole steroid therapy was 105 (range, 28–381) days. A total of 80.7% of patients (71/88) responded well to steroid treatment. In 63 patients, steroid treatment was successfully withdrawn, and treatment was completed. With an average of 283 days follow-up (range, 0–770 days), relapse was observed in 21 (33.33%) patients. Compared with patients with residual disease as shown by physical examination (PE), those with complete clinical remission (CCR) at the end of treatment had longer relapse-free intervals.

Conclusions: Steroids are the preferable breast-conserving option for IGM. Treatment with 20 mg methylprednisolone for an average of 1.5 months is usually required, and full steroid treatment might last for 3 months.

Keywords: Idiopathic granulomatous mastitis (IGM); steroid; breast; methylprednisolone

Submitted Aug 04, 2022. Accepted for publication Sep 14, 2022.
doi: 10.21037/gs-22-484
View this article at: https://dx.doi.org/10.21037/gs-22-484

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare but destructive inflammatory disease of the breast. The incidence of IGM has shown race disparity (1,2), and in recent years, the incidence of IGM has been reported greatly elevated (3).

IGM is a heterogeneous disease with a diverse spectrum of presentation, including painful or painless breast lumps, abscess, ulcers, and sinus. The optimal treatment for IGM remains unclear. As reported by previous studies, surgery, steroids, and observation are the primary treatment strategies for IGM (1,2). Although no clinical consensus is available

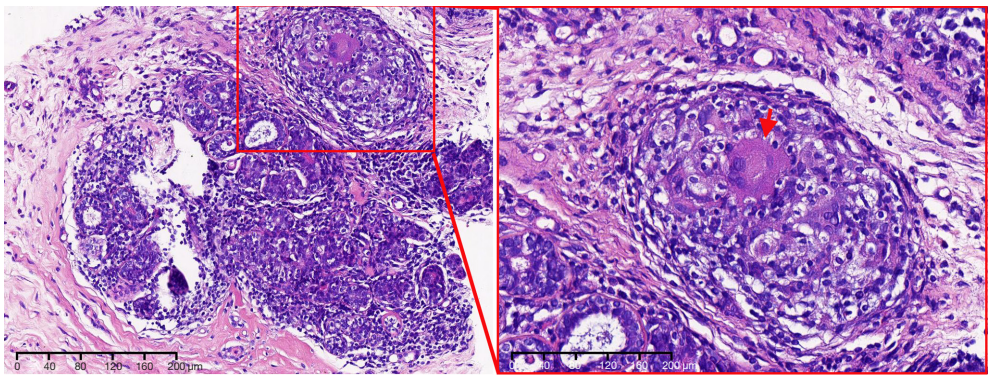

Figure 1 Idiopathic granulomatous mastitis was characterized as non-caseating granulomas of the lobules (red arrow), with Langhans multinucleated giant cells, polymorphonuclear leukocytes, and plasma cells (HE staining).

on the ideal therapeutic management, steroids have been advocated as the first-line treatment (2,4). However, the response rate of steroid varied significantly in reported studies. Furthermore, the decision criteria for steroid usage, initial dosage, as well as duration of steroid therapy remain uncertain in clinical practice (5,6). Management with steroids for IGM is still in the exploratory stage. Since the first report of high-dose corticosteroid treatment, which started with 30 mg/day prednisolone for at least 2 months (7), the reported dosages for steroids have varied, including 20–60 mg prednisone daily, tapered over 3, 5, or 6 weeks (8); 32 mg prednisolone daily for 2 weeks, tapered gradually (9); and 0.8 mg/kg methylprednisolone daily, tapered slowly according to the clinical and radiological response (10). Different strategies have resulted in conflicting outcomes. With no high-level evidence available, the Chinese expert consensus recommends empirical treatment with an initial dosage of 20 mg methylprednisolone for IGM treatment (4,11).

From Aug 2019, we prospectively collected the clinicopathological characteristics, treatment, and follow-up data of IGM patients presenting to our clinics. In the present cohort study, we aimed to report the response to steroids and explore the feasibility of steroids as a breast-conserving option for patients with IGM. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-484/rc).

Methods

Disease management and standardized data collection

From Aug 2019, for every IGM patient seeking treatment at the Department of Breast Surgery, West China Hospital, Sichuan University, a prospective standardized case report form (CRF) was used to collect the demographic information, obstetric history, clinical manifestations, concomitant diseases, physical examination (PE), and pathological, ultrasound, treatment, and outcome data. For each clinical visit, changes in symptoms, imaging, and PE were documented.

The diagnosis of IGM was confirmed using core needle biopsy (*Figure 1*). Breast granulomatous mastitis secondary to other diseases such as microorganism infection, sarcoidosis, polyangiitis, and polyarteritis nodosa were excluded. In our institution, non-surgical management comprises 3 categories: traditional Chinese herbal medicine, topical steroid treatment, and oral methylprednisolone (*Figure 2*). Antibiotics were applied simultaneously if necessary. Treatment response was documented prospectively. In the present cohort study, patients who treated with methylprednisolone for more than 1 week and had at least 1 follow-up visit were enrolled to evaluate the effectiveness of oral steroid treatment.

Referring to the expert consensus in China (4,11), in our study, oral steroid treatment was initiated with 20 mg methylprednisolone (Medrol, Pfizer). After complete remission (CR) or stable disease (SD) was achieved, the dose of methylprednisolone was tapered by 4 mg every 2–4 weeks. During steroid treatment, patients received regular outpatient clinical visits every 2–4 weeks. After treatment was finished, for patients with CR of breast lesions either by ultrasound or PE, a regular follow-up was referred every 6 months via outpatient clinical visits or telephone follow-up. For those with partial remission (PR) but stable breast lumps were still present, we considered

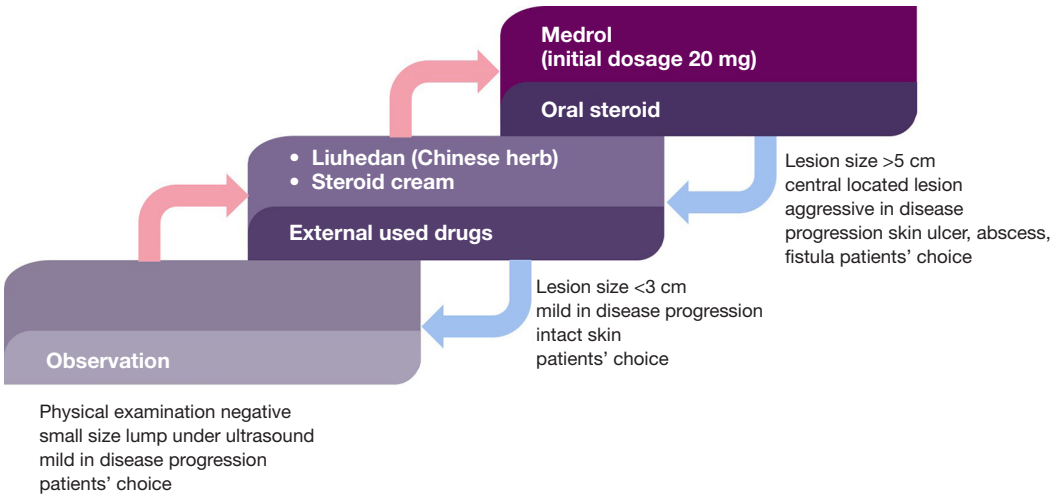

Figure 2 Current three-staged non-surgical management of idiopathic granulomatous mastitis at the Breast Disease Center, West China Hospital, Sichuan University, China.

surgery or observation based on the patient's choice. Patients with lesions that did not resolve with multiple courses of steroids or those who had major side effects from steroid treatment were referred for traditional Chinese medicine or excision.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of West China Hospital (No. 2021020A). All participants provided informed consent.

Primary assessment and statistical analysis

Breast lumps were measured using ultrasound. Considering the relatively large size, the location of the lump was defined according to its center. The primary endpoints were response rate (including complete and partial response) and CR rate. The secondary endpoints included time to CR, recurrence rate, and time to recurrence. Response to steroids was defined as relief in pain, swelling, and erythema, and a decrease in the size of the lesion after the first 2 weeks of treatment. Clinical complete remission (CCR) was defined as the absence of pain, swelling, erythema, tenderness, and lumps, close of the fistula and skin erosions after treatment by PE. Radiological complete remission (RCR) was defined as the disappearance of lumps on ultrasound. Time to CR was defined as the time interval from treatment initiation to termination. Relapse was defined as worsening of the disease during treatment or the reappearance of symptoms after the completion of treatment.

Data were collected in Microsoft Excel and statistical analysis was performed using the statistical software SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). A chi-squared test was performed for statistical analysis, and hazard ratio (HR) with 95% CI were used. A P value of less than 0.05 was considered significant.

Results

From Aug 2019 to Dec 2021, 156 patients diagnosed with IGM by core needle biopsy received treatment in the Department of Breast Surgery, West China Hospital, Sichuan University. A total of 88 patients who received oral steroids were included in this study (*Table 1*). The median age was 32 years old (range, 23–53 years old) at the time of diagnosis. Among all enrolled patients, 3 patients (3.4%) were nulligravida and 8 (9.1%) were nulliparity. Twelve women (13.6%) had no history of breastfeeding. Most patients had 1 child with a latency of 1 to 2 years between weaning and diagnosis of IGM. Ten patients (11.4%) reported taking an oral contraceptive within 3 months before the appearance of breast lesions, while 2 patients reported prior usage of psychotropic drugs. Three patients (3.4%) had concomitant hyperprolactinemia. One patient developed IGM 2 months after breast lipofilling.

Most patients complained of localized symptoms with unilateral breast involvement (87/88, 98.9%), including breast lumps (100%), light to moderate pain (71.6%), abscess formation (54.5%), erythema (48.5%), and skin sinus (19.38%). Most breast lumps were 2 to 5 cm in size

Table 1 Baseline characteristics of all enrolled patients

Factor	N	%
Age at diagnosis (years)		
<30	22	25.0
30–40	57	64.8
≥40	9	10.2
Gravidity		
G0	3	3.4
≥G1	81	92.0
Missing	4	4.5
Parity		
P0	8	9.1
≥P1	76	86.4
Missing	4	4.5
Breastfeeding time (year)*		
<1	54	71.1
≥1	19	25.0
Missing	3	3.9
Time since last breastfeed (years)*		
<1	15	19.7
1–2	21	27.6
2–3	12	15.8
3–4	13	17.1
≥4	12	15.8
Missing	3	3.9
Affected breast		
Left	49	55.7
Right	38	43.2
Bilateral	1	1.1
Lump size at the first visit (cm)		
<2	4	4.5
2–5	59	67.0
≥5	25	28.4
Affected quadrant		
Upper inner quadrant	20	22.7
Lower inner quadrant	6	6.8
Upper outer quadrant	34	38.6
Lower outer quadrant	12	13.6
Central region	16	18.2
Pain		
Painless	22	25.0
Light	42	47.7
Moderate to severe	22	25.0
Skin redness	43	48.9
Abscess	48	54.5
Sinus	16	18.2
Axillary node enlargement	26	29.5

*, 12 women with no history of breastfeeding were not included in this data.

and were located in the upper outer quadrant (38.6%) of the breast. About 18.2% of lumps were located in the central region. Among all involved breasts, only 5 breasts showed nipple retraction and 5 breasts had nipple discharge. General symptoms were rare, with only 4 patients presenting with fever and 2 presenting with erythema nodosum. Among all 88 patients, 12 patients had prior unsuccessful treatments.

Oral methylprednisolone was given at an initial dose of 20 mg/day. A total of 71 patients (80.7%) responded well, while 9 patients (10.2%) showed unresponsiveness to the treatment and 8 patients (9.0%) were lost to follow-up (*Figure 3A*). The median duration of 20 mg methylprednisolone treatment was 45 (range, 14–376) days. The dose was tapered by 4 mg every 2–4 weeks based on symptoms. During steroid withdrawal, disease relapse could occur and a subsequent 20 mg of methylprednisolone was re-administered to induce remission. Among the 71 patients who were responsive to methylprednisolone, 7 patients (9.9%) experienced relapse during steroid withdrawal and 1 patient refused to fulfill the treatment due to worries about side effects. For the remaining 63 patients who successfully completed steroid treatment, the median duration of methylprednisolone treatment was 116 (range, 28–284) days.

With an average of 283 (range, 0–770) days follow-up, 21 patients (33.33%) relapsed. The medium time to recurrence was 107 days. After relapse, topical steroids, oral steroids, or surgery were applied for selected patients. Limited by sample size, no risk factors for recurrence were identified.

At the end of steroid treatment, 30 patients (47.6%) achieved CCR by PE, among which only 18 patients (28.6%)

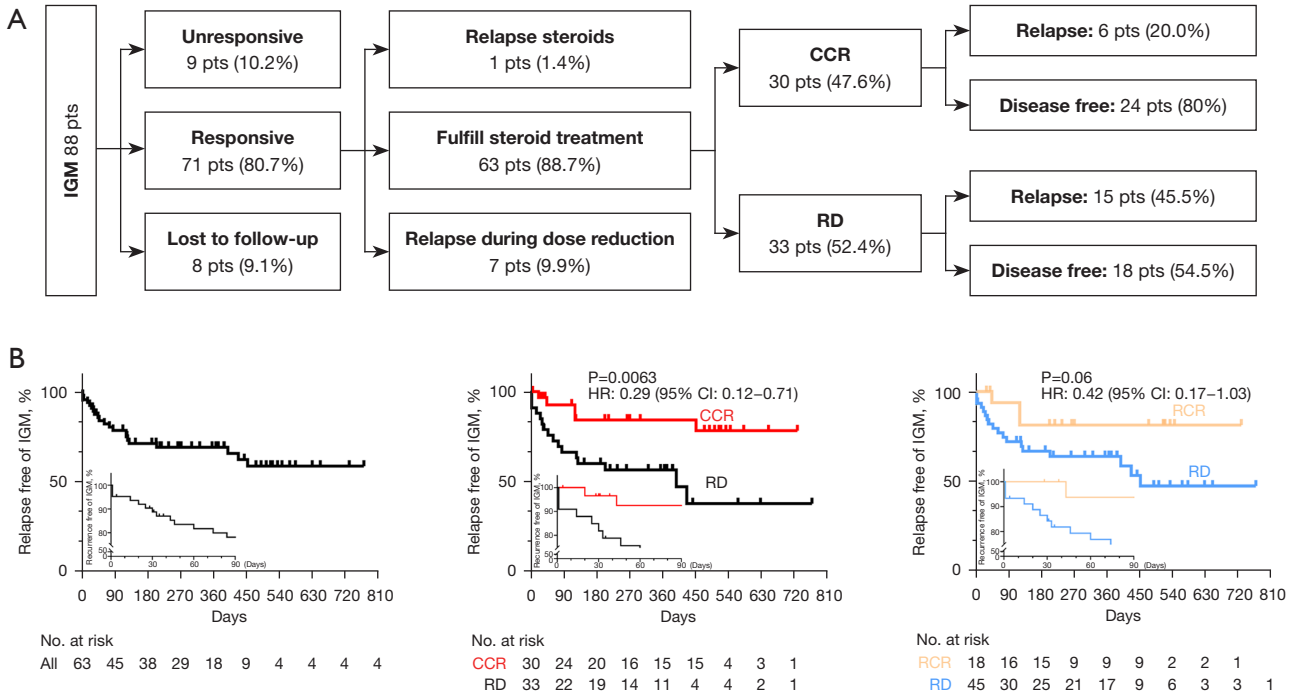

Figure 3 Study flow chart for IGM patients in our clinic (A) and disease relapse for all patients who completed oral steroid treatment (B). IGM, idiopathic granulomatous mastitis; CCR, complete clinical remission; RD, residual disease.

reached RCR by ultrasound. Compared with patients with residual disease (RD), those with CCR had a longer relapse-free interval (HR: 0.29; 95% CI: 0.12–0.71; P=0.0063) (*Figure 3B*). Similarly, those who achieved RCR also seemed to have a longer relapse-free interval, but the difference was not statistically significant, probably due to the limited sample size (HR: 0.42; 95% CI: 0.17–1.03; P=0.06). Additionally, more disease relapse was observed within 2 months after treatment termination.

In our experience, methylprednisolone was effective in reducing skin redness and chronic sinus (*Figure 4*). However, for large lumps, the symptoms might relapse during steroid withdrawal. The main side effects reported by patients were Cushing syndrome and elevated body weight.

Discussion

IGM is a rare, nonmalignant disease characterized by a diverse spectrum of presentation, aggressiveness in disease progression, and long-term therapy. IGM remains a therapeutic challenge. The clinical manifestations of IGM vary, from small lesions to whole breast involvement with abscesses and sinuses. Different clinical presentations require different treatments. Improper treatments may result in serious debilitation of the breast.

The treatment of IGM includes surgical and non-surgical procedures. In our data, a large proportion of patients presented with skin involvement (48.9%), central quadrant involvement (18.2%), and large lesion size (28.4% of patients with >5 cm in size) at their first clinical visit. Achieving acceptable cosmetic results after surgery is unlikely for these patients. In addition, recurrence remains a problem after surgery, with a reported recurrence rate varying from 23% to 50% (12-14). At the same time, as a benign disease without malignant tendency, mastectomy is apparently unacceptable. Oral steroids have been widely recommended as one of the non-surgical breast-conserving methods for IGM. However, controversies regarding steroid usage still remain to be solved. Therefore, a standard treatment for IGM needs to be been clarified. In our center, three-staged IGM management was proposed. Although the standard application of steroids remains unclear, we preferred those with large lesions in the breast, skin involvement, and acute stage of mastitis as the suitable candidates for steroids.

In the present study, we reported a significant regression effect of steroids for breast masses and fistulas. For large

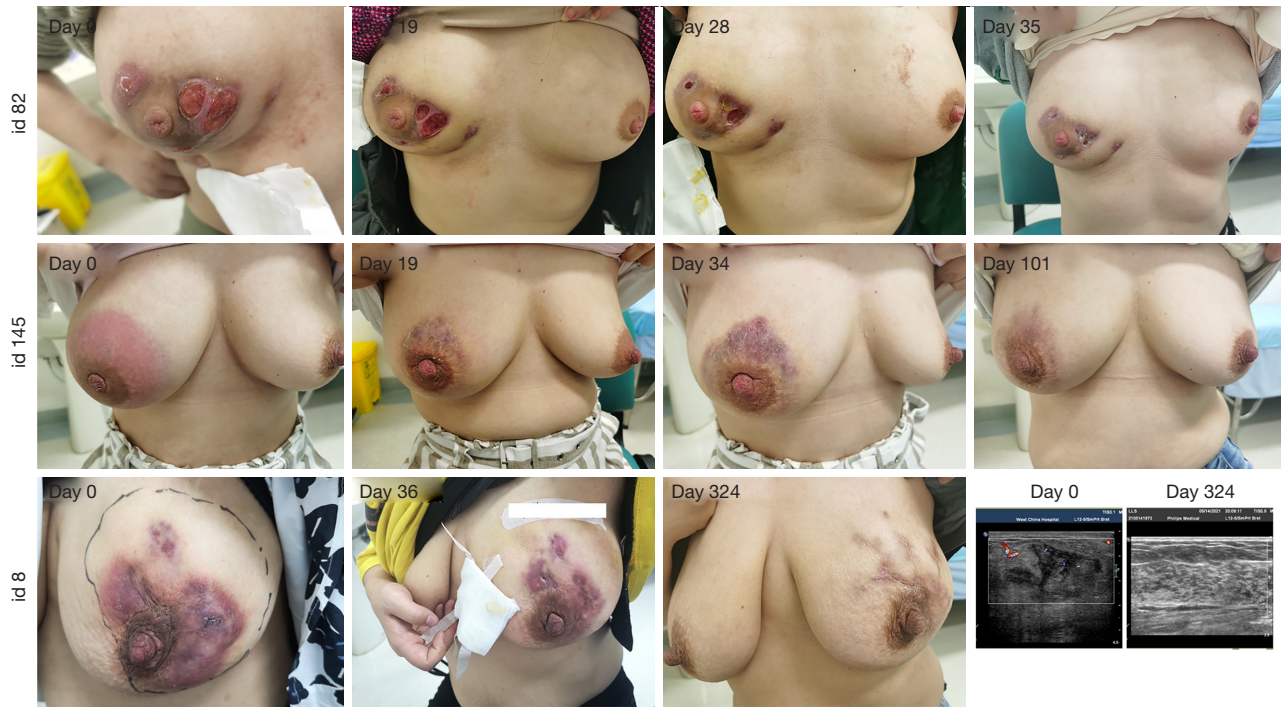

Figure 4 Responses to methylprednisolone for IGM treatment, including skin redness, abscess, and sinus. Patient ID 82, a 33-year-old woman with right IGM after antibiotic treatment at another hospital sought treatment at our clinic. Mastitis involved nearly the whole breast, with a centrally located skin ulcer and fistula (day 0). Surgery with wide excision did not achieve an acceptable cosmetic outcome. The fistula was completely closed after a month of treatment with methylprednisolone (day 35). Patient ID 145, a centrally located lesion with skin redness and edema was present (day 0). The lesion responded well (day 19), but relapsed during steroid withdrawal (day 34), and 20 mg of methylprednisolone was re-administered. At the same time, fine needle aspiration was applied for abscess drainage. Pigmentation and ultrasound detectable lesions were left. Patient ID 8, a 33-year-old woman with left IGM received repeated abscess incision drainage previously in another hospital (day 0). An excellent outcome was achieved by methylprednisolone treatment (day 36), with complete regression as shown by both PE and US. Only skin scars remained (day 324). IGM, idiopathic granulomatous mastitis; PE, physical examination; US, ultrasound.

lesions with skin involvement, steroids also provided the opportunity for surgery and breast conservation. Similar to other studies (9,15), we preferred non-surgical conservative treatments, as well as observation as the main strategy.

The endpoint for IGM treatment still remains unclear. In our study, a high response rate (80.7%) to oral steroids was observed, with the CR rate reaching as high as 47.6%. Similar studies have reported a CR rate of 0% to 86% (8,16,17). The initial characteristics of breast lesions can contribute to different CR rates. It was noteworthy that patients who achieved CR either by PE or ultrasound imaging showed a lower relapse rate, while non-CR patients showed a relapse rate as high as 40.2%. Whether to use CR or stable mass as the endpoint of steroid treatment still requires more study for confirmation. Considering the self-limiting nature of the disease (9), and to advocate for more conservative management for IGM, we preferred to leave a stable mass either identified by PE or ultrasound imaging after steroid treatment for follow-up. Surgery may be chosen for recurrently relapsed lesions to reduce the side effects of steroids. However, future high-quality randomized controlled studies are needed to confirm the value of surgery for IGM management.

Limited by the rarity of IGM, most of the reported studies are retrospective with a small sample size. The present prospective observation study collected data using CRF, which may be superior in study design and data reliability. However, the present study is a observational cohort study without control group. As IGM is highly heterogeneous and currently no standard treatment

available, the present study reported our experience of a 20 mg initialed usage of methylprednisolone, as recommended by the Chinese expert consensus (4). As high as 80.7% response rate and 47.6% CR rate, methylprednisolone showed a satisfactory management of IGM. Our data provides compelling evidence to make a definitive recommendation of oral steroids in the treatment of selective IGM patients. High-quality randomized controlled studies are needed to further improve the details of steroid management.

Conclusions

IGM is a rare but locally aggressive disease with a diverse spectrum of presentation. In this prospective cohort study, steroid therapy was an effective non-surgical option. With an initial dosage of 20 mg methylprednisolone for an average 1.5 months, the full duration of steroid treatment was 3 months.

Acknowledgments

We would like to thank our patients for their contribution to the present study.
Funding: This work was supported by the Key R&D project of Sichuan Provincial Science and Technology Department (22ZDYF1400).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-484/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-484/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-484/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of West China Hospital (No. 2021020A). All participants provided informed consent.

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Cite this article as: Tan QW, Zhang YN, Jia YP, Gou J, Lv Q, Yang XQ. Methylprednisolone for idiopathic granulomatous mastitis: a prospective observational cohort study. Gland Surg 2022;11(9):1538-1545. doi: 10.21037/gs-22-484