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IDIOPATHIC GRANULOMATOUS MASTITIS: MULTICENTER STUDY

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Abstract

Objectives: Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory breast disease of unknown etiology. There is no standardized treatment because its etiology is still unclear. In this multicenter study, we presented the demographic, treatment, and follow-up characteristics of IGM cases monitored by rheumatology clinics.

Material and Methods: This retrospective study was conducted in 13 different rheumatology centers. A total of 108 patients with IGM were included in the study. Demographic and clinical data were retrospectively obtained from patient files.

Results: The most commonly administered drugs were, in order of frequency, corticosteroid (CS) (91.7%), methotrexate (MTX) (74.1%), antibiotics (63%), non-steroidal anti-inflammatory drugs (41.7%), azathioprine (AZA) (13.9%), colchicine (5.6%), and tumor necrosis factor (TNF) inhibitors (0.9%). The most commonly used form of immunosuppressive (IS) treatment was the MTX and CS combination 78 (72.2%). The ratio of patients receiving CS alone was 19 (17.6%). The ratio of patients who were operated on only and did not use IS drugs was 6.5%. The ratio of patients who received no treatment was 2.8%. Among the drugs used, MTX and CS alone use were independent risk factors for relapse; (p=0.027, p=0.011, respectively). The relapse rate was higher in patients receiving CS alone.

Conclusion: IS drugs including CS, MTX, AZA, and TNF inhibitors seem to be efficient for treating IGM. CS alone use is associated with relapse, and the use of other IS drugs such as MTX is particularly effective in reducing relapse in IGM.

Keywords: Granulomatous mastitis, rheumatology, immunosuppressive drugs, corticosteroid, methotrexate

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory breast disease of unknown etiology. IGM frequently affects women of reproductive age and is characterized by the presence of non-caseating granulomas confined to the breast lobule (1,2). The mass presents with clinical findings such as erythema, swelling, fistula, nipple retraction, nipple discharge, abscess, and enlarged lymph nodes, and radiological findings such as hypoechoic lesions, calcifications, and asymmetric density increase (3). Because IGM may clinically and radiologically mimic acute breast infections or malignancy and hence cause a delay in diagnosis, pathological detection and exclusion of other causes are required for a definitive diagnosis of IGM. Other causes that should be excluded include tuberculosis, sarcoidosis, mycotic/parasitic infections, and other infective and autoimmune causes of granulomatous inflammation, such as granulomatous polyangiitis (GPA) (3,4).

The etiology of IGM is not clearly known, but risk factors may include trauma, hormones [oral contraceptives (OCS), pregnancy and childbirth], breastfeeding (which may involve both trauma and hormones), high prolactin (PRL) levels, infections (especially *Corynebacterium*), and autoimmunity (5,6). In addition, there appear to be geographical and ethnic differences in the prevalence of IGM (5,6). This geographical diversity suggests that there may be an underlying unidentified infectious trigger or genetic predisposition involved. Although antibiotics, corticosteroids (CS), and surgical excision are the primary treatment options for IGM, there is no standardized treatment because its etiology is still unclear (7,8). In this multicenter study, we aimed to present the demographic, treatment, and follow-up characteristics of IGM cases monitored by rheumatology clinics.

MATERIAL AND METHODS

This retrospective study was conducted in 13 different rheumatology centers. Ethics committee approval was obtained from by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

The informed consent form was obtained from each participant. A total of 108 patients whose physical examination findings were compatible with IGM and whose breast biopsy specimens were diagnosed as non-caseating granuloma on histopathological evaluation were included in the study. Patients over 18 years of age with clinical and radiological findings compatible with IGM and histopathologically verified granulomatous mastitis were included in this study, whereas patients with less than 6 months of follow-up, patients with underlying infection, granulomatous diseases such as tuberculosis, sarcoidosis, GPA, and malignancy were excluded.

Demographic and clinical data were retrospectively obtained from patient files. Age, gender, age at diagnosis, smoking status, oral contraceptive use, pregnancy and breastfeeding status, history of trauma, presence of infection, and autoimmune disease were recorded for each patient. The clinical findings were as follows: unilateral/bilateral presentation, mass, presence of skin changes (erythema, nipple inversion, hardening), pain in the breast, fistulization to the skin, nipple discharge, ulceration, axillary lymphadenopathy (LAP), arthralgia, arthritis, erythema nodosum (EN), fever, and weight loss.

Erythrocyte sedimentation rate, C-reactive protein, PRL, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-double-stranded DNA antibodies, rheumatoid factor, angiotensin-converting enzyme, and complement levels were obtained from the medical records of the patients. The findings from imaging methods used in diagnosis [breast ultrasound (US), breast magnetic resonance (MR) imaging or mammography], culture results, and biopsy results were recorded. Breast imaging findings were recorded using the terminology defined in the American College of Radiology Breast Imaging Reporting and Data System (9).

Treatment options administered [antibiotics, CS, immunosuppressive (IS) drugs, or surgical intervention], drug doses for each patient, duration of treatment, disease course, and outcomes were investigated. The IS drugs used [CS, methotrexate (MTX), azathioprine (AZA), and tumor necrosis factor (TNF) inhibitors] were recorded. The dose of CS was indicated as methylprednisolone (MP) or equivalent.

Treatment efficacy was evaluated as clinical improvement and partial or complete remission. Improvement in symptoms, physical examination findings, and acute phase reactants at the first-month visit was classified as clinical improvement; at least 50% improvement in clinical and radiological findings at the 3rd or 6th-month visits was classified as partial remission; and complete improvement in clinical and radiological findings at the 6th-month visit was classified as complete remission. Partial response is defined as a decrease in each clinical feature of at least half. If there was improvement in a single clinical parameter but not in others, it was not considered as partial remission. Radiological remission was defined as; the disappearance of all lesions on MR, US, or mammography. The presence of still-enhancing lesions was considered as radiological non-response.

Relapse was defined as disease recurrence after 3 months of remission. Persistent disease was considered as patients who

never achieved remission (3). If a new lesion developed (clinically or/and radiogically) in a patient who had been in remission for at least 3 months, this was evaluated as "relapse". If the patient developed a new lesion before remission was achieved, it was considered "non-response" to treatment.

Statistical Analyses

IBM SPSS 24 software for Windows (SPSS Inc., Chicago, Illinois) was used for statistical analyses. Descriptive statistics are presented as mean ± standard deviation and median (minimum-maximum) values for measured variables and frequency and percentage (%) for categorical data. Categorical variables of patients with and without relapse were compared using Pearson's chi-square test and Fisher's exact test, as appropriate. Factors related to relapse were evaluated by univariate and multivariate regression analyses. A value of $p<0.05$ was considered statistically significant.

RESULTS

Basic Characteristics and Clinical Features of Patients with IGM

A total of 108 patients were included in the study. The ratio of patients with pregnancy and with OCS use at the time of diagnosis was 3.7% (n=4) and 3.7% (n=4). The ratio of patients with less than 5 years since their last pregnancy was 35.8% (n=29). The ratio of patients with less than 5 years since the last lactation was 39.5% (n=32). The demographic data of the patients are shown in Table 1.

The most common clinical findings of patients with IGM at presentation were pain (99.1%), palpable mass (81.5%), stiffness (77.8%), erythema (76.9%), nipple discharge (50.9%), and axillary LAP (36.1%), in order of frequency. Both breasts were affected in 17.6% of the patients. The clinical findings of the patients at presentation are summarized in Table 2.

The frequency of laboratory and radiological findings and other diagnostic methods used in the diagnosis of patients with IGM are summarized in Table 3. Core biopsy was predominantly (75.9%) used in the diagnosis of patients. The ratio of patients who underwent culture was 51.8%. The most commonly used radiologic method in the diagnosis was ultrasonography, which was performed in all patients.

Treatment and Clinical Response in Patients with IGM

Table 4 summarizes the treatments administered to patients with IGM and their treatment responses. The most commonly administered drugs were, in order of frequency, CS (91.7%), MTX (74.1%), antibiotics (63%), non-steroidal anti-inflammatory drugs (41.7%), AZA (13.9%), colchicine (5.6%), and TNF inhibitors (0.9%). The most commonly used form of IS treatment was the MTX and CS combination 78 (72.2%). The ratio of patients receiving CS alone was 19 (17.6%). The ratio of patients who were operated on only and did not use IS drugs was 6.5%. The ratio of patients who received no treatment was 2.8%.

The evaluation of treatment responses revealed that 63% of the patients had partial remission and 9.3% had complete remission. There was no response to treatment in 8.3% of the patients, and relapse was observed in 15.7%.

Comparison of Patients with and without Relapse and Factors Affecting Relapse

When patients with and without relapse were compared, no difference was found between the two groups in terms of demographic data, laboratory findings, and radiological findings. Among the clinical findings, only the relapse rate was different in patients with fistulization and ulceration. 52.9% (9/17) of relapsed patients had fistulization compared with 24.1% (21/87) of non-relapsed patients (p=0.037). While 41.2% (7/17) of relapsed patients had ulceration, 47.1% (41/87) of non-relapsed patients had ulceration (p=0.034). The ratio of arthritis and EN was not different between relapsed and non-relapsed patients.

When patients with and without relapse were compared in terms of drugs used, it was found that 71.4% of patients with relapse used MTX, whereas 92.9% of patients without relapse used MTX. The relapse rate was 13.2% (10/76) in patients receiving MTX and 44.4% (4/9) in patients not receiving MTX (p=0.037). The relapse rate was 36.8% (7/19) in patients receiving only CS and 10/85 (11.8%) in patients not receiving CS (p=0.014). There was no significant difference between patients with and without relapse in terms of the other drugs used.

Factors affecting relapse were evaluated using univariate analysis. Among the clinical findings, the presence of inversion, fistulization, and ulceration were evaluated as prognostic factors; (p=0.017, p=0.021, p=0.017 respectively). Among the drugs used, MTX and CS alone use were independent risk factors; (p=0.027, p=0.011, respectively). When the factors found to be significant in univariate analysis were evaluated using multivariate analysis, CS alone use was found to be an independent risk factor. The relapse rate was higher in patients receiving CS alone.

Evaluation of Clinical Response According to the IS Drugs Used

Of the 95 patients who received CS, 8.4% (n=8) had no response, 67.4% (n=64) had partial response, 8.4% (n=8) had complete response, and 15.8% (n=15) had relapse. None of the 19 patients who received CS alone had no response, 47.4% (n=9) had partial

Table 1. Demographic characteristics of IGM patients	
Age, years, mean ± SD	36.6±6.7
Age at diagnosis, mean ± SD	34.3±6.1
Symptom duration, years, median (min-max)	1.5 (0.1-8)
Follow-up time, years, median (min-max)	2 (0.5-6)
Number of pregnancies, median (min-max)	2 (1-8)
Smoking status, n (%)	*Active smoker, 6 (5.6%) *Quit, 5 (4.6%) *Never smoked, 68 (63%) *Unknown, 27 (25%)
BMI, mean ± SD	27.2±4.1
Comorbidities, n (%)	
No	81 (75%)
Lung diseases	0 (0%)
Pulmonary hypertension	0 (0%)
Asthma	2 (1.9%)
Diabetes Mellitus	5 (4.6%)
Obesity (BMI>30)	5 (4.6%)
Hypertension	5 (4.6%)
Congestive heart failure	0 (0%)
Coronary artery disease	3 (2.8%)
Cerebrovascular event	0 (0%)
Renal failure	0 (0%)
Inflammatory bowel disease	1 (0.9%)
Psychiatric disorder	3 (2.8%)
Atopic eczema	1 (0.9%)
Liver disease	0 (0%)
Concomitant rheumatologic diseases	
Familial mediterranean fever	1 (1.2%)
Vasculitis limited to the skin	1 (1.2%)
Spondyloarthropathy	1 (0.9%)
Tuberculosis history	0 (0.0%)
History of sarcoidosis	0 (0.0%)
Oral contraceptive history, n (%)	*Never used, 61 (56.5%) *Using at the time of diagnosis, 4 (3.7%) *Used in the past, 12 (11.1%)
Intrauterine device history	*Never used, 63 (58.3%) *Using at the time of diagnosis, 11 (10.2%) *Used in the past, 3 (2.8%)
Pregnancy history	*None, 2 (1.9%) *Currently pregnant, 4 (3.7%) *Previous pregnancy, 77 (71.3%)
Time since the last pregnancy	*<5 years, 29 (26.8%) *>5 years, 21 (19.4%)
Time since the last lactation	*No lactation history, 0 (0.0%) *<5 years, 32 (29.6%) *>5 years, 17 (15.7%)

Patient percentages were calculated according to the total number of patients, IGM: Idiopathic granulomatous mastitis, SD: Standard deviation, BMI: Body mass index, min-max: Minimum-maximum, n: Number*

Table 2. Clinical characteristics of IGM patients

Clinical findings at diagnosis	n (%)
Erythema	83 (76.9%)
Nipple inversion	20 (18.5%)
Stiffness	84 (77.8%)
Palpable mass	88 (81.5%)
Pain	107 (99.1%)
Fistulization to the skin	30 (27.8%)
Ulceration	20 (18.5%)
Nipple discharge	55 (50.9%)
Axillary LAP	39 (36.1%)
Arthralgia	33 (30.6%)
Arthritis	3 (2.8%)
EN	14 (13.0%)
Arthritis + EN	5 (4.6%)
Fever	15 (13.9%)
Weight loss	8 (7.4%)
Affected breast	**n (%)** *Right only, 39 (36.1%) *Left only, 48 (44.4%) *Bilateral, 19 (17.6%)

IGM: Idiopathic granulomatous mastitis, LAP: Lymphadenopathy, EN: Erythema nodosum, n: Number*

response, 15.8% (n=3) had complete response, and 36.8% (n=7) had relapse. Clinical response was observed in 63.2% of patients who received only CS.

Of the 76 patients receiving MTX, 10.5% (n=8) had no response, 69.7% (n=53) had partial response, 6.6% (n=5) had complete response, and 13.2% (n=10) had relapse. Among patients receiving MTX, 76.3% showed clinical response. Among patients receiving AZA (n=15), 1 had no response, 11 had partial response, 1 had complete response, and 2 had relapse. Clinical response was observed in 80% of patients receiving AZA. The evaluation of clinical response according to the drugs used and the type of treatment administered is shown in Table 5.

DISCUSSION

Despite the increase in the frequency of patients diagnosed with IGM in recent years, available data on the clinical course and treatment of the disease are still limited. There is no consensus on the treatment of IGM because the number of prospective studies is limited and retrospective case series usually involve some patients. While patients with IGM were usually managed by general surgeons and gynecologists in the past, they have recently been increasingly managed by rheumatologists. In this study, we aimed to examine the follow-up and treatment of IGM

Table 3. Laboratory and radiologic findings and diagnostic methods used in patients with IGM (n=108)

Initial laboratory values	
ESR, mm/h, median (min-max)	30 (3-117)
CRP mg/L, median (min-max)	12 (2-96)
Prolactin, median (min-max)	14 (5-80)
Biopsy	*Excisional, 20 (18.5%) *Core, 82 (75.9%)
Culture	*No culture, 50 (46.3%) *Culture performed, no growth, 51 (47.2%) *Culture performed, the existence of growth, 5 (4.6%)
Radiology findings	
Breast US findings	*Mass-like areas with unclear borders, 50 (46.3%) *Phlegmonous changes, 1 (0.9%) *Increased density and fluid effusion, 83 (76.9%)
Mammography findings	*Focal asymmetry, 3 (2.8%) *Skin thickening, 2 (1.9%), *Scattered densities 11 (10.2%), *Masses and abscesses, 10 (9.3%)
Breast MRI	*Not performed, 75 (69.4%) *Performed-compatible with IGM, 30 (27.8%) *Performed-incompatible with IGM, 1 (0.9%)

IGM: Idiopathic granulomatous mastitis, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, US: Ultrasonography, MRI: Magnetic resonance imaging, min-max: Minimum-maximum, *

from the perspective of rheumatologists, and our experience in IGM follow-up and treatment is presented from the perspective of rheumatology.

Consistent with previous data, most patients in our series were young to middle-aged women, and the majority had a recent (last 5 years) history of child delivery and/or breastfeeding. Previous studies have indicated that pregnancy and breastfeeding are major factors responsible for IGM, especially in the reproductive age group, and may be risk factors for relapse (10-14). In our study, 75% of patients had a history of one or more pregnancies. Of the 81 patients with a history of pregnancy, information on the number of years before the diagnosis of IGM was available only in 50 patients, and 58% of these patients had a history of pregnancy within the last 5 years. Similar to our study, Barreto et al. (13) reported that 63% of patients had a history of pregnancy within the last 5 years. In our study, the ratio of patients with OCS use at the time of diagnosis was 14.8%, whereas it was 17%

in another study. In this study, elevated PRL levels were observed in 5 patients; however, none of the patients with elevated PRL levels had a history of pregnancy, breastfeeding, or any medication that might have increased PRL at the time of IGM diagnosis (15). In a previous study, five patients had elevated PRL levels without any underlying cause (13). In our study, pregnancy, breastfeeding, use of OCS, and elevated PRL were not found to be risk factors in terms of relapse.

The most common clinical findings in our study were pain, palpable mass, stiffness, erythema, nipple discharge, and axillary LAP. These findings are similar to other literature data. In our study, the concomitance of EN and arthritis was 4.6%. The incidence of EN was 13%, which is considerably higher than that in other cohorts. In a recent systematic review of 3060 cases, the incidence of EN was found to be 8% (15). The high incidence of EN and arthritis in our cohort may be partly explained by the fact

Table 4. Treatment and clinical response in IGM patients

Drugs used, n (%)	
NSAID	45 (41.7%)
Antibiotics	68 (63%)
Colchicine	6 (5.6%)
CS	95 (87.9%)
AZA	15 (13.9%)
MTX	80 (74.1%)
TNF inhibitors	1 (0.9%)
Initial CS dose	32 (4-80)
CS dose at the last visit	4 (0-24)
The total duration of CS, months, median (min-max)	10 (2-48)
Was CS treatment discontinued? n (%)	*No, 31 (28.7%) *Yes, 72 (66.7%)
Total IS duration, months, median (min-max)	9.5 (2-48)
AZA dose, median (min-max)	100 (100-150)
MTX dose, median (min-max)	15 (10-20)
Initial treatment approaches for patients, n (%)	*Surgery alone, 7 (6.5%) *IS treatment after failed surgery, 12 (11.1%) *Concomitant surgery + IS treatment, 4 (3.7%) *Patients receiving IS medication, 98 (90.7%) Medication use ratios of patients receiving IS treatment among all patients; *CS alone, 19 (17.6%), *MTX and CS, 78 (72.2%) *AZA and CS, 16 (14.8%) *TNF inhibitor + other IS, 1 (0.9%) *No medication, 3 (2.8%) Medication use ratios of patients receiving IS treatment; *CS alone, 19 (19.4%), *MTX and CS, 78 (79.6%), *AZA and CS, 16 (16.3%), *TNF inhibitor + other IS, 1 (1.02%)
Clinical response, n (%)	*No response, 9 (8.3%) *Partial response (at least 50% clinical and radiologic improvement at 3/6 months), 68 (63%) *Complete response (complete clinical and radiologic remission at 6 months), 10 (9.3%) * Relapse, 17 (15.7%)

IGM: Idiopathic granulomatous mastitis, NSAID: Non-steroidal anti-inflammatory drug, CS: Corticosteroid, AZA: Azathioprine, MTX: Methotrexate, TNF: Tumor necrosis factor, IS: Immunosuppressive, *, n: Number

Table 5. Clinical response according to drugs used and treatment modalities

	Non-response	Partial response	Full response	Clinical response (Partial + Full)	Relapse
CS alone (n=19) (%)	0 (0)	9 (47.3)	3 (15.8)	12 (63.2)	7 (36.8)
CS (n=95) (%)	8 (8.4)	64 (67.4)	8 (8.4)	72 (75.8)	15 (15.8)
Colchicine (n=6) (%)	0 (0)	4 (66.6)	0 (0)	4 (66.6)	2 (33.3)
MTX (n=76) (%)	8 (10.5)	53 (69.7)	5 (6.6)	58 (76.3)	10 (13.2)
AZA (n=15) (%)	1 (6.6)	11 (73.3)	1 (6.6)	12 (80)	2 (13.2)
MTX+ CS (n=74) (%)	8 (10.8)	50 (67.6)	6 (8.1)	56 (75.7)	10 (13.5)
AZA+ CS (n=16) (%)	1 (6.3)	12 (75)	1 (6.3)	13 (81.25)	2 (12.5)
Surgery alone (n=7) (%)	0 (0)	3 (42.8)	1 (14.3)	4 (57.1)	3 (42.8)
Postoperative IS (n=12) (%)	1 (8.3)	6 (50)	2 (16.6)	8 (66.6)	3 (25)
Surgery + IS at the same time (n=4) (%)	0 (0)	3 (75)	1 (25)	4 (100)	0 (0)
No treatment (n=3) (%)	1 (33.3)	2 (66.6)	0 (0)	2 (66.6)	0 (0)

CS: Corticosteroid, MTX: Methotrexate, AZA: Azathioprine, IS: Immunosuppressive, n: Number

that rheumatologists are more likely to identify these conditions. It may also suggest that IGM is a systemic inflammatory disease and that follow-up by rheumatologists may benefit the disease.

Although medical imaging provides important diagnostic information for the diagnosis of IGM, the definitive diagnosis of IGM relies on histological examination of tissue obtained from open biopsy (incision/excision) or core needle biopsy. Hovanessian Larsen et al. (16) used core needle biopsy in 46 of 48 cases of IGM in their series and reported success rates above 95%. When core biopsy fails to definitively diagnose IGM, an open biopsy is required to histologically confirm the presence of non-necrotizing granulomas. In our study, all patients underwent biopsy, and core biopsy was the most commonly used method in our cohort. Core biopsy was performed in 75.9% of the patients. The pathology results of 6 patients were not available.

In the literature, the optimal treatment for IGM is observation alone, antibiotic therapy, surgical resection, CS, and ISs (13). However, there is no standard treatment for IGM. It has been reported in many studies that patients with persistent symptoms are often prescribed different and multiple antibiotics (13,16-20). In our study, it was observed that 63% of the patients were prescribed antibiotics. Culture was performed in 55 (50.9%) of our patients, and growth was detected in 5 (0.9%). IGM is, by definition, a sterile inflammatory disease; therefore, antibiotic treatment is usually unsuccessful. It seems to be a more rational approach to administer antibiotic treatment according to microbiological culture results and to patients with growth.

Rheumatologists are often interested in granulomatous diseases and are more familiar with treatment options for ISs, which are not within the expertise of breast surgeons. To date, case series of CS, MTX, AZA, or TNF inhibitors have been reported in the treatment of IGM (7,15,18-22). Studies in the literature have shown that CS treatment may be effective in reducing mass size and improving abscess formation in patients with IGM. Some studies have indicated CS as a single drug or as first-line therapy before surgical excision because, in many publications, they allow for the reduction in the size of multiple and complicated lesions (7,15,19). Some authors recommend CS treatment only for refractory and recurrent cases.

Early data on the use of CS for IGM proposed an initial dose of 60 mg daily, but recent publications suggest that half this dose is equally effective (3,7,19). In our study, the starting dose of CS was found to be 32 mg MP or equivalent. Long-term and high-dose CS treatment may be associated with numerous side effects. In addition, studies in the literature report that a relapse rate of approximately 50% is possible when reducing the dose of CS (1). Although CSs have been used by many as first-line treatment for IGM, they are associated with significant risks when used long-term. Having additional should be is treatment options for IGM is important both in terms of preventing relapses and reducing the side effects of CS. In our study, the relapse rate in patients receiving CS alone was significantly higher than that in patients receiving CS and IS concomitantly. CS use alone is an independent risk factor for relapse.

In the literature, studies are showing the efficacy of MTX in reducing disease recurrence, suppressing inflammation, preventing complications, reducing the side effects of CS, and reducing the dose of CS in addition to achieving disease remission (3,15,22). In the study by Akbulut et al. (21) a total of 541 cases of IGM since 1972 were retrospectively analyzed and it

was shown that the addition of MTX therapy to CS therapy was effective in the management of IGM. Ringsted and Friedman (3) mentioned the rheumatologic approach in a series of 28 cases. In this study, patients treated with MTX had the highest relapse-free remission rates. In our study, the relapse rate of patients receiving MTX was 13.2% and that of patients not receiving MTX was 44.4%. Although our data show that patients treated with MTX have a higher remission rate, prospective, randomized studies comparing MTX with CS or other ISs with MTX would be very useful.

Similarly, Konan et al. (23) have shown the efficacy of AZA for treating IGM. In our study, remission was observed in 13 of 16 patients (81.3%) treated with AZA because of pregnancy or MTX-resistant disease. Among the treatments administered, the highest clinical response rates were observed in AZA plus CS treatment. The other treatment with the second highest response rate was the MTX plus CS combination. In terms of treatment modality, remission was observed in all patients who received both surgery and IS treatment simultaneously. Although a definite statement cannot be made because the number of patients who received surgery and IS treatment simultaneously was only 4, the combination of both appears to be increasing the response rates. In another study, surgery alone or in combination with CSs was found to have the lowest recurrence rates with 6.8% and 4%, respectively (24). In another study, 80% of patients treated with MTX, 42% of patients treated with CSs alone, and 66% of patients treated with CSs and surgery combined reported recurrence-free remission (3). In our study, patients who received postoperative IS treatment were found to be the second most frequent in terms of response to treatment, and the third most frequent in this respect were patients who only underwent surgery. In support of this finding, in our study, the highest relapse rate was found in patients who underwent surgery alone and who did not receive IS. The next highest relapse rate was observed in patients who received CS alone. When all the findings are evaluated together, it appears that the addition of ISs, especially KS, to the treatment is more effective in achieving emission and preventing relapses than surgery alone.

TNF inhibitors may also be effective for treating resistant cases (14). Cases treated with etanercept and adalimumab have been reported in the literature (25-28). In our study, one patient was treated with adalimumab. Because only one patient was using TNF inhibitors, it was not possible to evaluate the effect of TNF inhibitors in treatment based on this study. Further studies, including more cases, are needed to evaluate TNF inhibitors as effective agents in suppressing inflammation in IGM. In our study, colchicine was also used in 6 patients. Although it is not possible to conclude whether colchicine alone is effective, it may be one of the treatment options that might be considered in patients with EN or arthritis.

The appropriate duration of treatment in patients with IGM remains unclear. Previously, it has been noted that IS treatment should be continued until complete remission because otherwise, the relapse rate might be high. The commonly reported treatment duration is on average 12 months (29). In our study, the duration of IS treatment was found to be 10 (2-48) months.

Our study included patients who were followed up for at least 6 months. The mean follow-up period was 2 years. The follow-up period in our study was quite long, and the relapse rate was quite low compared with the data reported in the literature. The most powerful feature of this study is that it is multicenter and the number of patients is quite high compared with other data in the literature.

The main limitation of our study is its retrospective design. Except for one prospective case series, all data in the literature are retrospective case series (10). Further studies with larger samples and prospective designs are needed to confirm the efficacy of systemic IS therapies for treating IGM.

CONCLUSION

IS drugs including CS, MTX, AZA, and TNF inhibitors seem to be efficient for treating IGM. CS alone use is associated with relapse, and the use of other IS drugs such as MTX is particularly effective in reducing relapse in IGM.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

Informed Consent: The study was designed retrospectively.

Authorship Contributions

Surgical and Medical Practices: S.E., M.S.A., L.A., M.A.B., B.K., S.S.K., Concept: S.E., M.Ş.A., O.C., Ş.K.E., M.A.B., B.K., S.S.K., Design: S.E., M.S.A., M.Ş.A., S.Z., O.C., F.A., O.Z., Ö.K., E.İ., S.Y., L.A., Ş.K.E., H.B., M.A.B., Y.S., A.K., H.A., B.K., S.S.K., Data Collection or Processing: S.E., M.S.A., M.Ş.A., S.Z., O.C., F.A., O.Z., Ö.K., E.İ., S.Y., L.A., Ş.K.E., Y.S.,H.B., M.A.B., A.K., H.A., B.K., S.S.K., Analysis or Interpretation: S.E., M.Ş.A., F.A., Ö.K., Ş.K.E., H.B., M.A.B., Y.S., A.K., B.K., S.S.K., Literature Search: S.E., S.Z., O.C., O.Z., S.Y., H.B., M.A.B., Y.S., A.K., B.K., S.S.K., Writing: S.E., M.S.A., M.Ş.A., E.İ., M.A.B., Y.S., H.A., B.K., S.S.K.

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