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Risk Factors for Idiopathic Granulomatous Mastitis Recurrence after Patient-Tailored Treatment: Do We Need an Escalating Treatment Algorithm?

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Keywords

Granulomatous mastitis · Idiopathic · Risk factors · Surgical treatment · Steroids · Combined treatment

Abstract

Objective: Idiopathic granulomatous mastitis (IGM) is a rare, relapsing, benign inflammatory breast disease. Due to the conflicting etiology and differential diagnosis, the effect of varied treatment regimens on high recurrence is controversial. Therefore, we aimed to report our clinical experience in determining risk factors for recurrence after patient-tailored treatment. ***Methods:*** This study evaluated 122 patients diagnosed with IGM according to sociodemographic characteristics, reproductive history, clinical presentation, time of diagnosis and radiological examinations, treatment management, and outcomes. The patients were classified into three groups based on curative treatment settings: medical therapy alone, surgery alone, and combined therapy. ***Results:*** The rates of patients receiving medical therapy alone, surgical therapy alone, and combined therapy were 23, 15.6, and 62.4%, respectively. Low vitamin B_{12} levels, accompanying rheumatological disease, complaints-fistulae, number of complaints ≥3, presence of erythema nodosum, multicentricity, and treatment modality had a significant effect on disease recurrence ($p < 0.05$). The effect on IGM recurrence was 2.8 times greater for the patients with lower vitamin B_{12} levels, 4.5 times greater for those with rheumatological disease, 3.3 times greater for those with fistulae, 2.4 times greater for those presenting with ≥3 complaints, 2 times greater for the presence of multicentricity, 2.3 times greater for the presence of erythema nodosum, and 4.5 times greater for the patients receiving medical therapy alone. ***Conclusion:*** Describing a low-risk patient profile can be an alternative while choosing monotherapy methods. For IGM patients at high risk of recurrence, an escalating treatment system may be effective in preventing relapses.

Introduction

Idiopathic granulomatous mastitis (IGM) is a rarely observed, benign chronic inflammatory breast disease of unclear etiology, which clinically and radiologically simulates malignant epithelial tumors of the breast [1, 2]. This condition was first described by Kessler and Wolloch [3] in 1972, and a 2020 meta-analysis reported 21 publications incorporating more than 50 patient series and a total of 970 cases treated with different methods, including surgical excision, steroids, abscess drainage, antibiotics, and observation [4]. Since both clinical and radiological findings suggest a suspicion of breast carcinoma, the diagnostic and therapeutic dilemma renders the process difficult for both the patient and the clinician. Most of the affected patients are generally young women of reproductive age either with a recent history of pregnancy and lactation or oral contraceptive use in the last 2 years. The correlation between IGM and breastfeeding, as well as oral contraceptive use has been debated, but has never been proven by any study. Rare cases have been reported in elderly patients with accompanying rheumatological or immune-suppressive diseases, including rheumatoid arthritis, Sjogren's syndrome, and sarcoidosis. IGM gen-

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erally presents as a unilateral breast mass, sometimes with skin involvement as fistulae and axillary lymphadenopathy [5, 6]. It can be seen in any quadrant of the breast, except in the subareolar region [7, 8]. It is a disease of unknown etiology but an autoimmune chain reaction is implicated in the etiopathogenesis. Local trauma, local irritants, or viruses have been speculated as agents triggering this immune process [5, 7]. The pathological demonstration of non-caseous granulomas is the characteristic of the disease and considered as a diagnostic criterion for IGM after the exclusion of other potential infectious (tuberculosis, mycoses) and non-infectious causes (sarcoidosis, Wegener granulomatosis, foreign body reactions) [8]. There is no well-described effective diagnostic protocol or treatment model for IGM yet. Medical treatment with corticosteroids and methotrexate, even with colchicine, wide surgical excision of the lesion with clear margins, and more drastic measures such as total mastectomy are treatment options that can be considered [9–12]. Recurrent attacks associated with monotherapy methods have led researchers to combine treatment methods in order to keep patients in remission. Here, we report a series of 122 cases of IGM managed according to their clinical presentation with either monotherapy or combined therapy models with the aim to review and describe the clinical and pathological features and report our clinical experience in determining risk factors for recurrence after patient-tailored treatment.

Materials and Methods

Patients and Methods

This study was carried out by reviewing the records of 122 women aged 29–47 years diagnosed with IGM who presented to the general surgery and internal medicine departments of our hospital between November 2012 and January 2019. Only patients who were treated medically or surgically and were followed up by the same breast surgeon were enrolled in the study. The patients' medical records were retrieved from the hospital database and analyzed respectively. The exclusion criteria were mastitis with a known etiology (tuberculous, fungal, foreign body, eosinophilic and periductal type), any kind of neoplastic disease history, immunosuppressive drug use for an already known autoimmune disease, and incompliance with treatment or follow-up. The diagnosis of IGM was made based on typical physical and radiological findings, mostly by ultrasonographic findings with or without additional imaging methods according to the patients' disease status, and confirmed histopathologically by ultrasound-guided multiple core-needle biopsies of the breast lesions, biopsy specimens taken from the abscess wall during surgical drainage, or excisional biopsies of the breast masses. The presence of non-caseating granulomatous inflammation on breast lobules without an identifying etiology was the main pathological criterion for the diagnosis of IGM. The tissues obtained via core, incisional, or excisional biopsy were stained with hematoxylin and eosin, Gomori methenamine silver, and the Gram stain, as well as for acid-fast bacilli using paraffin-embedded sections. The samples were cultured to exclude infectious causes due to bacteria and tubercular bacilli. A retrospective chart review of the 122 patients, including patient sociodemographic characteristics, reproductive history, clinical presentation, diagnosis time and radiological investigations, therapeutic management, outcomes, and follow-up, was undertaken. The main outcomes of this study were the rates of cure and recurrence and underlying factors that defined the outcome. Cure of disease was defined as the state of complete healing in the whole breast parenchyma without any inflammatory sign accompanying an acceptable wound healing process, proven by both a thorough physical and ultrasonographic examination. Recurrence of disease was defined as the reappearance of inflammatory symptoms, including pain, swelling, redness, fluctuation, and abscess formation more than 3 months after the complete healing of breast parenchyma following appropriate treatment. The selection of treatment was based on some criteria, including the dimension and extent of the lesions, severity of symptoms, patients' general well-being, and personal choices. All patients were classified into three groups based on the curative treatment settings: medical therapy alone (the initial steroid dose prescribed was 0.8 mg/kg/day oral methylprednisolone for the first 2 weeks, tapered down gradually by 0.1 mg/kg/day weekly), surgery alone (wide local surgical excision), and combined medical and surgical treatment (steroid treatment prior to or following surgery). At the end of the eighth week, physical and radiological examinations were undertaken to evaluate the patients in the medical therapy alone group for the regression of breast lesions to determine whether they required surgery and evaluate those in the surgery alone group for residual breast lesions to determine whether they required steroid treatment.

Statistical Analysis

The data were collected by clinical physicians from the relevant departments, transferred to Microsoft Excel, edited, and prepared for statistical analysis. Descriptive statistics were used to describe sociodemographic data, reproductive history, clinical presentation, diagnosis time and radiological investigations, therapeutic management, and outcomes. The descriptive statistics are expressed as numbers and percentages for categorical variables, and mean, standard deviation (SD), and minimum and maximum values for numerical variables. All quantitative data are presented as percentage and median ± interquartile range (IQR) values in the tables. The Kolmogorov-Smirnov normality test, Mann-Whitney U test, *t*-test, χ^2 test, and logistic regression analysis were utilized in the analyses. Data analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics v.26.0.

Results

A total of 122 IGM patients' demographic and baseline characteristics are shown in Table 1. The median age was 34.1 (29–47) years, and the median follow-up was 32.5 (19–67) months. Most of the patients reported having >8 years of education (74.6%). The great majority of patients were found to have had at least a single live birth and breastfed for at least 6 months (86.9 and 86.8%, respectively). Regular menstruation (68%) was more common than irregular menstruation (23.8%), and only 8.2% of the evaluated women were in the post-menopausal period. Of the study sample, 79.5% declared no concomitant disease whereas autoimmune thyroiditis was found to be the most common disease accompanying IGM (8.2%), followed by

Table 1. Frequency distribution

Variable	
Median age, years (range)	34.1 (29–47)
Median follow-up time, months (range)	32.5 (19–67)
Educational status, *n* (%)	
Illiterate	6 (4.9)
Primary school	25 (20.5)
Secondary school	62 (50.8)
University or higher	29 (23.8)
Smoking, *n* (%)	
Absent	72 (59.0)
Present	50 (41.0)
Number of births, *n* (%)	
None	16 (13.1)
Single	40 (32.8)
2 or more	66 (54.1)
Lactation, *n* (%)	
None	16 (13.1)
Less than 18 months	48 (39.3)
More than 18 months	58 (47.5)
Menstruation, *n* (%)	
No menstruation	10 (8.2)
Regular	83 (68.0)
Irregular	29 (23.8)
Accompanying disease, *n* (%)	
None	97 (79.5)
Autoimmune thyroid disease	10 (8.2)
Diabetes	6 (4.9)
Rheumatological disease	9 (7.4)
Pathological diagnosis method, *n* (%)	
Tru-cut biopsy	73 (59.8)
Abscess drainage	39 (32.0)
Surgical specimen	10 (8.2)
Treatment method, *n* (%)	
Medical therapy alone	28 (23.0)
Surgery alone	19 (15.6)
Combined	75 (62.4)
Additional imaging, *n* (%)	
None	40 (32.8)
Mammography	40 (32.8)
MRI	42 (34.4)

other rheumatological diseases (7.4%) and diabetes mellitus (4.9%). The most commonly used pathological diagnostic method was core-needle biopsy (59.8%), and the remainder of the patients were diagnosed during the surgical process based on either abscess drainage (abscess wall biopsy, 32%) or surgical excision of the target lesion (8.2%). Twenty-three percent of the patients (n = 28) received medical therapy alone, 15.6% (n = 19) were treated with surgical drainage or excision, and 62.4% (n = 75) received combined therapy consisting of both surgical excision and medical treatment. Only 32.8% (n = 40) of the patients had no other radiographic examination other than ultrasonography before the treatment, whereas 32.8% (n = 40) had undergone mammography and 34.4% (n = 42) had MRI before the planned treatment was initiated.

Table 2 shows that among the demographic characteristics, only the number of live births was found to be a remarkably associated factor with disease recurrence (p = 0.036). On the other hand, of the clinical and treatment characteristics of the patients analyzed according to the presence of recurrence, vitamin B_{12} and vitamin D levels of the patients at the time of diagnosis, symptom duration, and lesion size were found to be significantly associated with disease recurrence (p = 0.011, p = 0.002, p = 0.038, and p = 0.020, respectively). When the tables were examined a statistically significant relationship was observed between the presence of recurrence and the number of births, multicentricity, erythema nodosum, complaint-fistulae, number of complaints ≥3, and treatment method according to the χ^2 analysis ($p < 0.05$). When the accompanying diseases and treatment method that might be associated with recurrence were examined, it was determined that the recurrence rate was higher (50%) in patients with autoimmune thyroid disease, those with rheumatological disease, and those in the medical monotherapy group (Table 3). The logistic regression model revealed that the variables of low vitamin B_{12} levels at the time of diagnosis, accompanying rheumatological disease, presence of fistulae, number of complaints ≥3, presence of erythema nodosum, multicentricity, and treatment modality, had a significant effect on disease recurrence ($p < 0.05$; Table 4). Accordingly, the triggering effect for IGM recurrence development was 2.8 times greater for the patients with lower vitamin B_{12} levels at the time of diagnosis, 4.5 times greater for those with accompanying rheumatological disease, 3.3 times greater for those presenting with fistulae, 2.4 times greater for those presenting with three or more complaints, 2 times greater for the presence of multicentricity, 2.3 times greater for the presence of erythema nodosum, and 4.5 times greater for the patients receiving medical therapy alone. The model accurately classified two-thirds of the cases that had recurrence (positive predictive value = 75%).

Discussion

IGM is a rarely observed, benign, chronic self-limiting inflammatory condition of the breast, first described as a new clinical entity in 1972 by Kessler and Wolloch [3] and characterized by non-caseating granulomas in the pathological examination of affected tissue [12]. It usually affects parous women at reproductive age, most commonly those of Hispanic and Asian origin; however, to date, series with only few numbers of patients have been reported worldwide and in all races [6, 13]. Although the exact etiology is still not clearly defined, it is mostly considered to be an autoimmune-based disorder. The autoimmune pathogenesis proposed by Keller and Wolloch is also sup-

Table 2. Demographic characteristics of the patients according to the presence of recurrence

Variable	Total	Recurrence		*p*
		absent	present	
Age, years	34.3±6.1	34.33±6.8	34.25±5.07	0.959[a]
BMI	25.0±3.17	25.16±3.29	24.87±3.68	0.663
Educational status				0.456[b]
Illiterate	6 (4.9)	6 (100.0)	0 (0.0)	
Primary school	25 (20.5)	21 (84.0)	4 (16.0)	
Secondary school	62 (50.8)	53 (85.5)	9 (14.5)	
University or higher	29 (23.8)	22 (75.9)	7 (24.1)	
Smoking (yes)	50 (41.0)	41 (82.0)	9 (18.0)	0.805[b]
Number of births				**0.036**[b]
None	16 (13.1)	13 (81.3)	3 (18.8)	
Single	40 (32.8)	36 (90.0)	4 (10.0)	
2 or more	66 (54.1)	53 (80.3)	13 (19.7)	
Lactation				0.900[b]
None	16 (13.1)	13 (81.3)	3 (18.8)	
Less than 18 months	48 (39.3)	41 (85.4)	7 (14.6)	
More than 18 months	58 (47.5)	48 (82.8)	10 (17.2)	
Menstruation				0.307[b]
No menstruation	10 (8.2)	10 (100.0)	0 (0.0)	
Regular	83 (68.0)	69 (83.1)	14 (16.9)	
Irregular	29 (23.8)	23 (79.3)	6 (20.7)	
Family history (yes)	15 (12.3)	12 (80.0)	3 (20.0)	0.711[b]

Data are presented as the mean ± SD or *n* (%). [a] *t*-test. [b] χ^2 test. Bold values are statistically significant at $p < 0.05$.

ported by some authors within the scope of ductal epithelial damage theory, suggesting that ductal epithelial damage leads to the transition of luminal secretions to the connective tissue, local inflammation, macrophage and lymphocyte migration, resulting in a granulomatous inflammatory response [14, 15]. However, so far no triggering factor has been clarified in the development of ductal epithelial damage.

IGM presents with a progressive painful breast lump usually accompanied by nipple retraction, skin thickening, sinus formation, and axillary lymphadenopathy [8, 16, 17]. The first imaging modality preferred for the diagnosis is ultrasonography. Additionally, mammographic findings generally resemble those of the malignant tumors of the breast, with the most common being focal asymmetric density and irregular masses with ill-demarcated borders. Therefore, it should be kept in mind that no radiological imaging modality can adequately exclude underlying malignancy or diagnose IGM, and there is always a need for a confirmatory histopathological diagnosis [17, 18].

Although described as a self-limiting condition, the optimal treatment of IGM is still controversial. The medical literature describes a wide range of treatment modalities, with a particular emphasis being placed on the autoimmune origin of the disease since a favorable response to steroid and immunosuppressive treatment is observed, especially in patients with extensive or recurrent disease or those with extramammary manifestations like erythema nodosum or arthritis [15]. Only few articles have described specific treatment protocols for IGM, and the optimal treatment has not yet been established [7, 19–21]. Most patients in the current study were already receiving antibiotherapy, and some had undergone abscess drainage before diagnosis; therefore, antibiotherapy was preferred only for the patients with mixed secondary aerobic and anaerobic infections during the follow-up process [7]. The available treatment options of IGM include close follow-up, immunosuppressive drugs, and surgical excision. Patients with uncomplicated IGM may continue being asymptomatic for a certain time without requiring treatment, but most patients suffer from one of the symptoms of pain, spontaneous wound drainage, or sinus formation; thus, they mostly seek medical help [7, 13, 14]. Lai et al. [22] reported spontaneous resolution without treatment in 50% of cases in their study, with a mean interval of complete healing of 14.5 months (range 2–24). On the other hand, corticosteroid treatment was found to be effective in extensive and recurrent cases with no organism in wound drainage [23, 24]. The use of corticosteroids was first proposed by Dehertogh et al. [10] based on the autoimmune nature of the disease. Several case series have also reported corticosteroid treatment success in IGM, and most have claimed that corticosteroids should be started at a dose of

Table 3. Clinical and treatment characteristics of the patients according to the presence of recurrence

Variable	Total	Recurrence		*p*
		absent	present	
Vitamin B_{12} level, pg/mL	186.43±10.17	226.88±14.65	145.54±8.17	**0.011**[a]
25-OH vitamin D level, ng/mL	19.01±3.25	17.33±2.11	24.28±3.65	**0.002**[a]
Symptom duration, months	3.76±2.56	3.04±2.4	4.65±2.61	**0.038**[a]
Lesions, *n*	1.74±0.8	1.55±0.8	1.85±0.81	0.079
Largest lesion, mm	39.07±15.73	38.26±16.39	41.05±15.99	**0.020**[a]
Recurrence time, months		–	4.6±2.28	–
Accompanying disease				**<0.001**[b]
None	97 (79.5)	83 (85.6)	14 (14.4)	
Autoimmune thyroid disease	10 (8.2)	7 (70.0)	3 (30.0)	
Diabetes	6 (4.9)	5 (83.3)	1 (16.7)	
Rheumatological disease	9 (7.4)	7 (77.8)	2 (22.2)	
Treatment method				**<0.001**[b]
Medical therapy alone	28 (23.0)	20 (50.0)	8 (50.0)	
Surgery alone	19 (15.6)	13 (68.4)	6 (31.6)	
Combined	75 (62.4)	70 (93.6)	5 (6.4)	
Multicentricity	54 (44.3)	38 (70.4)	16 (29.6)	**0.021**[b]
Erythema nodosum	26 (21.3)	10 (38.4)	16 (61.5)	**0.001**[b]
Complaints				
Mass	102 (87.1)	87 (85.3)	15 (14.7)	0.319[b]
Pain	90 (73.8)	74 (82.2)	16 (17.8)	0.588[b]
Discharge	31 (25.4)	25 (80.6)	6 (19.4)	0.585[b]
Fistula	47 (38.5)	36 (76.6)	11 (23.4)	**0.032**[b]
Lymphadenopathy	30 (24.5)	23 (76.7)	7 (23.3)	0.261[b]
Number of complaints				**0.016**[b]
<3	60 (49.2)	54 (52.9)	6 (30.0)	
≥3	62 (50.8)	48 (47.1)	14 (70.0)	

Data are presented as the mean ± SD or *n* (%). [a] *t*-test. [b] χ^2 test. Bold values are statistically significant at $p < 0.05$.

Table 4. Logistic regression analysis of the presence of recurrence

	B	SE	Wald	df	*p*	Exp(B)	PPV, %	NPV, %	Accuracy, %
Constant	−2.949	0.948	9.680	1	**0.002***	0.052	75.0	85.6	85.2
Births, *n*			4.714	2	0.095				
None	−1.926	1.007	3.656	1	0.056	0.146			
Single	−0.442	0.793	0.311	1	0.577	0.643			
Vitamin B_{12}	2.112	0.734	3.638	1	**0.002**	2.783			
Rheumatological disease	2.312	0.783	5.734	1	**0.004**	4.536			
Complaint – fistula	1.189	0.563	4.456	1	**0.035**	3.285			
Number of complaints ≥3	2.117	0.934	8.729	1	**0.012**	2.423			
Multicentricity	2.745	0.884	9.651	1	**0.002**	2.064			
Erythema nodosum	1.726	0.876	4.645	1	**0.003**	2.332			
Medical treatment (alone)	1.517	0.480	9.974	1	**0.002**	4.557			

Dependent: recurrence; independent: investigated variables. Bold values are statistically significant at $p < 0.05$. Backward method.

1 mg/kg per day and tapered slowly according to clinical response [13, 19, 25]. The unfavorable part of this treatment modality is the high recurrence rates after stopping or decreasing the dose of steroids [19, 25]. It would be wiser to use corticosteroid treatment either after surgical excision or abscess drainage in complicated and resistant cases or in initially unresectable lesions with extensive disease infiltrating more than one quadrant [15, 18]. Balancing the risks and benefits of steroid therapy remains a matter of debate due to the lack of data on this subject.

A wide local excision can be an appropriate treatment method for patients with smaller lesions, and it may have both therapeutic and diagnostic value in determining the follow-up method for each patient. Some studies have suggested that the recurrence rate with surgical treatment is higher than that with steroid treatment [2, 24]. Recurrence rates of 5–50% are reported after the surgical excision of lesions. Wide excisions with negative margins are better than abscess drainage or limited excision alone since there is a higher tendency to relapse after these procedures [14–16, 25]. In a retrospective review of cases over 25 years, Al-Khaffaf et al. [11] showed that regardless of therapeutic intervention, which included steroids, antibiotics, and surgical intervention alone or in combination, the condition took approximately 6–12 months to resolve completely.

The main aim of all treatment methods is not only achieving the complete well-being of breast parenchyma with minimal cosmetic deformities, but also preventing recurrent attacks. The current study was designed to analyze the factors that could have triggered recurrent attacks after appropriate treatment and define the importance of a patient-tailored therapy protocol. When we evaluated the descriptive data and disease characteristics, low vitamin B_{12} levels at the time of diagnosis, accompanying rheumatological disease, presence of fistulae, three or more symptoms, erythema nodosum or multicentricity, and treatment with medical monotherapy significantly increased the risk of recurrence. Examining the previously published literature reviews, we determined a lack of clinical risk assessment analyses which may be helpful to promote a treatment algorithm [25–27]. Based on the findings of our study, identification of these high-risk patient groups may be valuable to develop an algorithm for a patient-tailored therapy protocol. Patients presenting with accompanying rheumatological diseases, low vitamin B_{12} levels, breast fistulae, more than three complaints at the time of diagnosis, and multicentric disease were found to have the highest risk of developing IGM recurrence after the completion of treatment. In our experience with a case series of 122 patients, our recurrence rate in the combined modality group was lower than the rates reported in similar previous studies conducted with a relatively low number of patients [17, 26–28]. In our study, only 5 of the 75 patients treated with combined treatment had recurrence (6.4%); however, this rate increased to 40 and 46.1% in the monotherapy groups treated with either steroids or surgery alone, respectively. Comparing our results with those of the previously published literature reviews, combined treatment methods seem to be more effective than any monotherapy protocol.

Based on the data obtained from the current study, we concluded that IGM recurrence is directly related to the clinical presentation and the severity of the disease at the time of admission for seeking medical help. The increased risk of recurrence identified in patients with breast fistulae, more than three complaints at the time of diagnosis, erythema nodosum, and multicentric disease may be attributed to a delay in treatment. This finding also shows a distinct parallelism with the literature suggesting the severe inflammation as the most effective factor in recurrence [16, 17, 27]. In addition, considering that the symptoms vary depending on the time of admission to the hospital, it is obvious that the treatment protocols initiated in early stages of the disease would be more effective in preventing recurrences. On the other hand, vitamin B_{12} deficiency and history of accompanying rheumatic disease seem to be more specific parameters in determining high-risk profile patient groups, as they are not affected by the time of admission and the severity of the disease. This situation brings to mind the idea of determining the treatment algorithm by scoring the specific and non-specific factors affecting the disease recurrence in IGM, which still lacks a patient-based treatment methodology.

To proceed one step further in risk strategy management, the hypothesis derived from the study that vitamin B_{12} deficiency detected at the initial stages of disease has a remarkable effect on complete remission and recurrence rates led the authors to conduct future research focusing on adjunctive parenteral vitamin B_{12} replacement in newly diagnosed patients. Since vitamin B_{12} deficiency has an endemic distribution in the regions where IGM is encountered frequently, we believe that patients with IGM should be encouraged to take supplemental doses of vitamin B_{12} with both prophylactic and therapeutic intention. According to the obtained study results, determining the initial level of vitamin B_{12} would be helpful in establishing the treatment protocol, and may reduce the rates of unnecessary invasive surgical procedures if properly supplemented in suitable patient groups that ended up with complete remission proven by radiological methods.

When all data are analyzed and compared in an up-to-date meta-analysis, the decision making in a patient-based escalating treatment algorithm seems to begin with the past medical history and the already available vitamin B_{12} levels and patients should be followed consistently in 3-week periods, follow-up being more prominent for patients admitted with aforementioned clinical presentation [4]. Although surgical excision was reported to carry lowest recurrence rates in many patient series, it would be wiser to classify the patients before treatment planning. In order to fill this gap in the literature, we find it appropriate to conduct new studies by grouping the disease with a large patient series with a well-established scoring system and evaluating the effectiveness of the treatment over a long period of time.

Despite having the largest number of histopathologically proven IGM patients from a single center and being one of the largest series in the current medical literature, this study also has certain limitations. The retrospective cohort design may be considered as a disadvantage in comparing the treatment results in terms of disease recurrence. In addition, the patients were not categorized at the beginning of the study according to the severity of the disease since there is no such scoring system in IGM; thus, the patients presenting with more severe disease may have been treated more intensively compared to those presenting with a few complaints. On the other hand, the patient population enrolled in the study attended their follow-up sessions regularly, and the treatment plans were revised according to their positive or negative response during this process.

As previously described in the literature, steroid treatment decreases the size and extension of IGM lesions; thus, there is a better chance of complete healing without recurrence after the complete excision of residual lesions. In light of our results, the determination of risk profiles can help identify the patients that can benefit from monotherapy, and we recommend an escalating treatment system for IGM patients, especially those carrying a high risk of recurrence. Prospective randomized studies focusing on the autoimmune basis of IGM are needed to compare patient-tailored monotherapy and combined treatment approaches to prevent frustrating recurrent attacks.

Statement of Ethics

All participants were informed about the purpose of the study and signed the written informed consent form. The study protocol was approved by the Institutional Review Board of the Medipol University (10840098-604.01.01-E.7222, IRB No.127), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest related to the publication of this work.

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Author Contributions

Concept, P.B.; design, P.B, D.A.; supervision, F.A.; resources, P.B., D.A; data collection and/or processing, P.B., D.A, F.A.; analysis and/or interpretation, D.A, F.A; literature search, P.B, F.A; writing manuscript, P.B, D.A.; critical review, P.B.

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