Medical Treatment and Prognosis

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Since idiopathic granulomatous mastitis was first described, an ideal treatment approach has not yet been established. One of the most important reasons for this is that the etiopathogenesis is not yet clearly understood and the heterogeneous clinical appearance within the patient population [1–4]. In recent years, the etiopathogenesis is based mostly on autoimmune and immune dysregulation which raises the question of whether IGM is a surgical or a systemic disease [5–9]. Consequently, the use of immunosuppressive drugs such as corticosteroids and methotrexate has increased for the treatment of IGM [10–16].

In this chapter, the treatment and management approaches of IGM and the optimal treatment options recommended are discussed in the light of the literature.

1 Treatment Approaches

Today, it is possible to examine the treatment approaches used in IGM under three main headings. These are conservative treatment approaches, surgical interventions, and combined treatment approaches (Table 1) [3, 4, 17, 18].

An optimal treatment option for IGM has not yet been established. Idiopathic granulomatous mastitis is a benign disease with chronic granulomatous inflammation. It has a very heterogeneous clinical spectrum, and therefore, it may not be correct to apply the same treatment approach to every patient. It will be much more appropriate to choose the treatment option according to the patient. Therefore, a classification for IGM is needed to determine the optimal

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Table 1 Treatment approaches used until today

Treatment approaches
Conservative approaches
Wait and watch
Only antibiotics
Nonsteroidal anti-inflammatory drugs
Immunosuppressive therapy
Corticosteroid
Systemic corticosteroids
Local corticosteroid administration
Topical
Intralesional
Combine local (topical + intralesional)
Combine administration (local + systemic)
Methotrexate
Azathioprine
Mycophenolate mofetil
Traditional medicine
Others
Colchicine
Etanercept
Minocycline
Bromocriptine
Platelet-rich plasma
Surgical procedures
Drainage
Excision
Mastectomy
Combine treatment approaches
Drainage + antibiotic
Drainage + corticosteroid (systemic or local)
Excision + antibiotic
Excision + corticosteroid (systemic or local)
Drainage + excision + antibiotic
Drainage + excision + corticosteroid (systemic or local)

personalized treatment approach. Two clinical classifications have been proposed for IGM [19–21] and these classifications proposed by Irkorucu [20] and Yaghan et al. [21] are similar. While the classification proposed by Irkorucu [20] can be used for all granulomatous mastitis, the classification suggested by Yaghan et al. [21] is a clinically based classification of IGM. Recently, Kaviani and Vasigh [22] proposed a classification system which has the subtitle of extramammarian manifestations (see Chap. 5).

1.1 Conservative Approaches

1.1.1 Wait and Watch

Idiopathic granulomatous mastitis is a chronic granulomatous inflammation around the lobules that can be self-limiting and resolving [4, 17, 23–25].

Lai et al. [25] reported that four of eight patients with IGM who did not undergo any surgical intervention had spontaneous remission on an average of 14.5 months (range, 2 to 24 months) and no recurrence was observed on long-term follow-up.

Bouton et al. [23] analyzed 37 IGM patients retrospectively, 36 of whom were Hispanic. Thirty-two (86%) of these patients were uninsured. In this study, 27 patients were followed up without excision and the disease was found to be resolved. However, drainage and/or antibiotic treatment was applied to patients who did not undergo excision. The resolution times of lesions were found to be 0–6 months in 11 patients (41%), 6–12 months in 12 patients (44%), and > 12 months in four patients (15%). The mean time for resolution of these patients was 7.4 months (range, 0–20 months). Recurrence was observed in only three patients (8%). The authors found that the lesions could resolve spontaneously with observation. In addition, they emphasized that their findings suggest that management of IGM with close observation is feasible in some selected patients.

In the study by Davis et al. [24], 120 patients with IGM were analyzed retrospectively. Most of the patients (92%) were Hispanic. Antibiotics were prescribed to 35 patients (29%) and analgesics to 27 patients (23%). While no incision or drainage was required in 87 patients (72%), one incision or drainage was performed in 21 patients and more than one incision or drainage in 12 patients (10%). The authors reported that the lesions resolved with observation in 112 patients and the resolution times ranged between 0 and 20 months (mean: 5.1 months). About two-thirds of patients recovered in the first 6 months, 23% between 6 and 12 months, and 5% in more than 12 months. The relapse rate in this study was 16%.

In the study by Cetinkaya et al. [26], 118 IGM patients were analyzed retrospectively. Their treatment schemes were no treatment (n = 50, 42.4%), corticosteroid treatment (n = 36, 30.5%), antibiotics (n = 21, 17.8%), excision (n = 9, 7.6%), and azathioprine (n = 2, 1.4%). Varying numbers of drainage were applied to 54 patients. While the recovery time of patients without any treatment ranged between 1.3 and 13.8 months (mean recovery time: 5.1 months), this period varied between 0.8 and 9.8 months (mean recovery time: 3.9 months) in patients receiving corticosteroid treatment. Interestingly, there was no statistically significant difference between patients without any treatment and those who received corticosteroid treatment by means of recovery times. The authors found recurrence in 14 patients (11.9%) in their study. Considering the initial treatment of patients with recurrence, 8 patients (57.1%) had corticosteroid treatment, 4 patients (28.5%) had antibiotics, 1 patient (7.1%) was given no treatment, and 1 patient (7.1%) underwent excision. In conclusion, this study emphasized that in case of an abscess or collection, it is appropriate

to give a chance to the self-limiting nature of the disease with the addition of drainage and antibiotic therapy.

In our previous study [17], it was observed that 11 of 134 IGM patients did not receive any treatment and only one patient relapsed (9%). This suggests that although the number of patients included in this group is small, a wait-and-watch approach may be an option in selected IGM patients.

In conclusion, it should be kept in mind that IGM can be self-limited and can resolve spontaneously. However, if a wait-and-watch approach is to be applied, the patient should be well informed and possible increased recovery time should be explained. The wait-and-watch strategy may be a good alternative approach for patients whose lesion size does not exceed 2 cm in patterns A and B according to the classification suggested by Yaghan et al. [21].

1.1.2 Antibiotics Only

The role of antibiotics for the treatment of IGM could not be clearly established yet [4, 27]. It is important that the clinical presentations of IGM are very heterogeneous. The general approach to the treatment of IGM is the use of antibiotics, especially in patients with signs of inflammation or an abscess-like appearance [3].

Failure to recognize the microbiological cause is an important problem in patients who have signs of inflammation on the skin or have an abscess-like appearance [17]. Kıvılcım et al. [28] investigated the bacteria mentioned in the study using a universal DNA primer in paraffin blocks of patients with IGM. The authors concluded that bacteriological agents are not the primary cause of IGM etiology.

The most comprehensive study on the use of antibiotics for IGM treatment is the study of Aghajanzadeh et al. [29]. They used antibiotics such as cloxacillin, cephalexin, ciprofloxacin, or clindamycin to treat all of their patients for approximately 3 weeks, but in only 3% of the patients, an improvement in symptoms and signs was seen.

A study by Li [30] reviewed 75 IGM patients. Thirty-one of these patients had a history of antibiotic use before admission. While 23 of these patients who received antibiotic treatment did not respond to antibiotics, eight patients were observed to have a partial response. Pathogenic microorganisms could complicate IGM and the study emphasized that the use of antibiotics may partially improve at least these symptoms or signs.

The ideal approach to the use of antibiotics is to document the potential microorganism. However, since this is not possible in IGM, empirical antibiotics are generally used. The most preferred antibiotics are cloxacillin, cephalexin, clindamycin, flucloxacillin, ciprofloxacin, or doxycycline, which are effective for gram-positive cocci [3, 29]. Apart from that, the use of rifampicin and azithromycin has also been reported in the literature [31–33].

In conclusion, although the microorganism cannot be documented in patients with IGM, considering that IGM may be complicated secondarily by a pathogenic microorganism emphasized by Li [30], empirical antibiotic treatment can be used especially in patients with signs of inflammation in the skin or with abscess-like lesions.

1.1.3 Nonsteroidal Anti-Inflammatory Drugs

In IGM, the use of corticosteroids has increased in recent years and it brings to mind the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of IGM. However, experience with the use of NSAIDs in patients with IGM is very little compared with corticosteroids [34–38].

Studies with NSAIDs as a treatment of IGM by Kaviani et al. [36, 37] are very instructive. Kaviani et al. [36] evaluated 20 IGM patients between 2007 and 2011. All patients used empirical antibiotics (at least 2 weeks) and NSAIDs (at least 2 months). They used corticosteroids for resistant or early relapse patients. They achieved excellent or good control in 15 out of 20 patients. Two patients needed corticosteroids. In another study by Kaviani et al. [37], NSAIDs were preferred as the first line for the treatment of 41.8% of 374 IGM patients. The most used NSAID in this study was naproxen. In the treatment of patients with NSAIDs, 31.5% had a *complete response* and 59.2% a *moderate response*, while 6.2% of patients did not respond to treatment, and 3.1% of patients progressed. The recurrence rate was 16.9%. The authors achieved dramatic and acceptable response to NSAIDs, although NSAIDs have been used in moderate and severe IGM patients. They emphasized that NSAIDS were as effective as prednisolone in moderate to severe cases.

In conclusion, when deciding the treatment option for a patient with IGM, if there are contradictions to the possible side effects of corticosteroids and other immunosuppressive drugs, any NSAID treatment may be used once approved by a rheumatologist. In addition, the use of NSAIDs in IGM treatment is a good research topic requiring further studies.

1.1.4 Immunosuppressive Treatment

Corticosteroids

Recently, DeHertogh et al. [39] first described the increasing interest in corticosteroid therapy for the treatment of IGM.

According to the application methods of corticosteroids in IGM treatment, it can be classified under three main headings: systemic, local (topical, intralesional, or both), or combined (systemic and local) corticosteroid therapy.

Systemic Corticosteroid Therapy

Nowadays, since DeHertogh et al. [39] first used systemic corticosteroids for the treatment of IGM, there has been an increasing interest on the use of corticosteroids for IGM treatment ([11, 15, 25, 32, 34, 37, 38, 40–75]).

Firstly, DeHertogh et al. [39] administered prednisone at a dose of 60 mg/day in an IGM patient. At the end of 3 weeks, the lesions resolved, and the treatment lasted approximately 4 months. They reported no recurrence in the patient but did not provide any information with regards to the possible side effects of corticosteroid in their article.

To date, corticosteroid therapy in IGM treatment has mostly been related to systemic corticosteroid therapy by oral application. Some of these studies or case report(s) are summarized in Table 2. As shown in this table, most corticosteroids used were intermediate acting such as prednisone, prednisolone, or methylprednisolone. Dexamethasone, a long-acting corticosteroid, was used in only two publications [43, 73]. In both publications, dexamethasone was preferred as a loading drug and the treatment was continued with prednisolone. If dexamethasone in these two studies was ignored, prednisone or prednisolone was the most used drugs.

Table 2 Summary of some studies using only systemic corticosteroid therapy in IGM treatment

Author(s)	Drug and dose	Duration of treatment	Recovery time	Recurrence	Side effect(s)
Atak et al. [42]	Methylprednisolone – 0.8 mg/kg/days – Tapered down each week at a rate of 0.1 mg/kg/day	8 wks	Unkn	No	Unkn
Binesh et al. [43] The patient with arthritis and erythema nodosum	– Dexamethasone 12 mg/day (1.5 days) – After that, prednisolone 30 mg/day – After 1 week the dose was halved and slowly tapered	Unkn	Unkn	No	Unkn
Boufettal et al. [34]	Prednisone 1 mg/kg per day for 2 months with gradual dose reduction	2 mos	Unkn	4/5 patients	Unkn
Casteren et al. [44]	Patient 1, methylprednisolone – 32 mg/day (2 wks) – 16 mg/day, (2 wks) – 8 mg/day, (2 wks)	6 wks	2 wks	No	Hot flushes Some nausea
Cetin et al. [10]	Methylprednisolone – 0.8 mg/kg/day – tapered slowly according to the clinical and radiological response		11.7 ± 5.5 wks (4–24 wks)	20.7%	Weight gain Hirsutism Iatrogenic Cushing
Chirappapha et al. [46]	Corticosteroid (dose unknown)	Unkn	114.5 days (42–416)	1/6 patients	Unkn
DeHertogh et al. [39]	Patient: prednisone 60 mg/day	4 mos	3 wks	No	Unkn

(continued)

Table 2 (continued)

Author(s)	Drug and dose	Duration of treatment	Recovery time	Recurrence	Side effect(s)
Deng et al. [47]	Prednisolone – 30 mg/day, (the 1st and 2nd wks) – 20 mg/day, (the 3rd wk) – 10 mg/day, (the 4th wk) – 5 mg/day, the 5th and 6th wks	Unkn	1.5 Mos (1.5–9)	18.5%	Unkn
Erozgen et al. [48]	Prednisolone – 32 mg/day, (2 wks) – Tapered in 2 mos	2.5 mos	Unkn	1/25 patients (4%)	Weight gain
Gopalakrishnan Nair et al. [49]	Prednisolone – Loading dose of 0.5 mg/kg – Tapered to maintenance dose of 5 mg/day, by 4 weeks – Maintenance dose for 6 mos	7 mos	Unkn	1/23 patients (4.3%)	Unkn
Goulabchand et al. [50]	Patient: Prednisone – 35 mg/day (1 mo) – Tapered in 3 mos	4 mos	Nearly 1 mo	No	Unkn
Hashmi et al. [52]	Patient: Prednisolone – 20 mg/day	Unkn	Unkn	Unsuccessful	Unkn
Hwang et al. [54]	Patient: Prednisolone – 40 mg/day	2 wks	2 wks	Unsuccessful	Unkn
Karanlik et al. [55]	Methylprednisolone – 0.5 mg/day (2–4 wks) – Then tapered down slowly for 4 wks	Unkn	Unkn	30%	Cushingoid appearance Hirsutism

(continued)

Table 2 (continued)

Author(s)	Drug and dose	Duration of treatment	Recovery time	Recurrence	Side effect(s)
Katz et al. [56]	Patient 1: Prednisone 40 mg/day (Treatment was changed to methotrexate) Patient 2: Prednisone 40 mg/day Patient 3: Prednisone 30 mg/day Patient 4: Prednisone 20 mg/day	10 days Unkn 1 year Unkn	6 wks Unkn Unkn	No No Yes (dose at 5 mg/days	Corticosteroid-induced diabetes mellitus No No No
Kaviani et al. [37]	Prednisolone (dose unknown)	Unkn	13.9 ± 10.4 wks	24.8%	Unkn
Mahmodlou et al. [59]	Prednisolone – 100 mg/day (2 wks) – 50 mg/day (2 wks) – 25 mg/day (2 wks) – 10 mg/day (2 wks) – 5 mg/day (1 wk)	9 wks	Unkn	3/33 patients (nearly 9%)	Weight gain Acne
Montazer et al. [15]	Prednisolone – Low dose (5 mg/day) – High dose – 50 mg/day (3 days) – 25 mg/day (3 days) – 12.5 mg/day (3 days) – 5 mg/days (afterwards)	2 months	3.25 ± 1.75 mos 5.28 ± 3.93 mos	37.5% 0%	Unkn
Mizrakli et al. [38]	Prednisolone (dose unknown)	Unkn	Unkn	No	Unkn
Naraynsingh et al. [62]	Prednisolone – Patient 1: 60 mg/day – Patient 2: 80 mg/day	Unkn Unkn	8 wks 6 wks	No No	Unkn Unkn

(continued)

Table 2 (continued)

Author(s)	Drug and dose	Duration of treatment	Recovery time	Recurrence	Side effect(s)
Néel et al. [63]	Corticosteroid 40 mg/day, (20–60 mg/day)	15 mos (4–117)	Unkn	46%	Unkn
Olsen and Dilaveri [64]	Corticosteroid (dose unknown)	Unkn	Unkn	Unsuccessful	Unkn
Oran et al. [65]	Prednisolone – 32 mg/day, (2 wks) – Tapered in 6 wks	Nearly 2 mos	Unkn	5/25 patients (20%)	No
Pandey et al. [66]	Prednisone – 40 mg/day (2–4 wks) – tapered by 5–10 mg every 2–4 weeks based on symptom relief	Unkn	159 days Q1 = 120 days Q3 = 241 days	23%	Unkn
Ruiter et al. [67]	Patient: Prednisone – 60 mg/day (2 wks) – Tapered to 20 mg/day (6 wks) – 2.5 mg/wk. – Tapered in 5 mos	5 mos	2 Mos	Yes	Moon face Weight gain
Sakurai et al. [68]	Prednisolone 60 mg/day	7.5 mos (1–10)	4–10 Mos	1/8 patients	
Salehi et al. [32]	Prednisolone – 60 mg/day (2 wks) – 40 mg/day (8 wks) – Tapered for 6 mos	8 Mos	Unkn	6.2%	
Sheybani et al. [70]	Prednisone – 0.5–1 mg/kg/day (3–4 weeks) – 5.0 mg per week until prednisone tapered to 10.0–15.0 mg/day – Continue with more slow taper by 5.0 mg every 2–3 weeks until treatment is discontinued	Unkn	Unkn	20% (tapering period)	
Skandarajah et al. [71]	Prednisolone 0.5 mg/kg/day	Unkn	3 mos (2–24)	4/8 patients	

(continued)

Table 2 (continued)

Author(s)	Drug and dose	Duration of treatment	Recovery time	Recurrence	Side effect(s)
Su et al. [72]	Patient 1, prednisolone – 0.6 mg/kg/day (28 days) – Tapered in 3 wks	1.5 Mos	1 mo	Yes	
Wang et al. [73]	Dexamethasone 5 mg/day (5 days) Prednisolone – 20 mg/day (1 wk) – 15 mg/day (1 wk) – 10 mg/day (1 wk) – So on, until treatment cessation	Unkn	258 days	22.7%	
Yabanoglu et al. [74]	Methylprednisolone – 0.8 mg/kg/day (1 Wk) – Thereafter 0.1 mg/kg/day	Unkn	6 Mos (1–15 Mos)	9/44 patients (nearly 20%)	
Yilmaz et al. [75]	Methylprednisolone – 30 mg/days (3 mos) – Tapered in 3 days	3 Mos	Unkn	12.6%	
Yuksekdag [76]	Prednisolone – 64 mg/day (4 wks) – Tapered in 2 wks	6 wks	6 wks (1–10)	14.9%	No

mo(s), month(s); wk(s), week(s); unkn, unknown; w, with; w/o, without

Low or high doses of corticosteroid was preferred depending on the type of corticosteroid. Preferred doses for prednisolone range from 20 to 80 mg/day, but the initiating dose is often around 0.5–1 mg/kg/day. The dosage of prednisone was also similar. The initiating dose for methylprednisolone was 0.5–0.8 mg/kg/day. After the initial dose, tapering and discontinuation was applied according to the clinical and/or radiological response.

There are some questions that need to be answered in systemic corticosteroid therapy.

(i) "Should systemic corticosteroids be used in every IGM patient?" The answer to this question is probably "No," given that a watch-and-wait strategy is a good approach in some IGM patients [26].

(ii) "Considering patients who recur during corticosteroid dose tapering or very soon after cessation, is there a need for maintenance corticosteroid therapy? If so, how long should this period be?" Systemic corticosteroids may be a treatment option in patterns C and D in the classification of Yaghan et al. [21], or

types II, III, and IV in the classification of Irkorucu [19, 20]. If recurrences occur during cessation or after the termination of therapy, the drug doses can be reduced by spreading it over a longer period of time or combined corticosteroid therapy regimens can be used.

(iii) "What about the side effects associated with corticosteroids?" The side effects of corticosteroids are well documented. Reported side effects were weight gain, hot flashes, nausea, hirsutism, Cushing syndrome, moon face, acne, hyperglycemia or diabetes mellitus, and poor sleep [10, 44, 48, 55, 56, 59, 67, 70, 73].

In conclusion, systemic corticosteroid therapy is a good treatment option in some selected patients with IGM. Given as a single dose, early in the morning, it does not suppress the circadian peak in cortisol secretion in the next morning. In order to minimize systemic steroid-related side effects, corticosteroid treatment should be given as a single dose between 06.00 and 07.00 in the morning after breakfast.

Local Corticosteroid Therapy

Topical Corticosteroid Therapy

Altintoprak [77] successfully applied topical corticosteroid treatment in IGM. The author noted that low-dose prednisolone (30 mg/day) and topical Prednasinolone pomade (twice a day, four times per week) were administered because of the patient's peptic ulcer history. The author reported that the patient was in remission in the fifth week of the treatment, but recurrence occurred after 8 weeks. It was stated that topical corticosteroid treatment application to this patient was successful and no other recurrence was observed again.

In another study of the same center [78], they applied topical corticosteroids (twice a day, on alternate days for 4 days, with a subsequent interval of 3 days, for 12 weeks) to 11 IGM patients. All patients were successfully treated, recurrence developed in only two patients at the fifth and eighth months. These patients were also treated with topical corticosteroids. In another retrospective study from the same center, the effectiveness of topical corticosteroid treatment was again proven successful [79].

Cetin et al. [10] conducted a very important randomized, prospective study on topical corticosteroid therapy for the treatment of IGM. Moreover, 124 IGM patients were evaluated and divided into three groups according to treatment approaches: systemic corticosteroid treatment (0.8 mg/kg/day per oral), topical corticosteroid treatment (Prednasinolone 0.125% pomade, twice a day in weekdays), and combined corticosteroid treatment (0.4 mg/kg/day per oral + Prednasinolone 0.125% pomade, twice a day in weekdays). They found that the outcomes of all treatment groups were similar and the lowest corticosteroid-related side effects were observed in the topical corticosteroid group. In addition, they concluded, "topical steroids would be among first-line treatment options of IGM."

Intralesional Corticosteroid Therapy

Recently, a new application of local corticosteroids, intralesional corticosteroids, has been described for the treatment of IGM [80–82].

Alper et al. [80] administered methylprednisolone acetate, a depo-corticosteroid, and injected into the perilesional fibroglandular tissue. They achieved a complete response in 89.3% of their patients and a partial response in 10.7%, with no steroid-related side effects.

Kornfeld and Mitchell [81] administered 40 mg/1 mL triamcinolone, an intermediate-acting drug, mixed with 3 mL 2% lidocaine into the affected areas of the breast in a 7-month pregnant woman. The authors concluded that intralesional injection of steroid can provide significant symptomatic relief to patients.

In Toktas et al.'s [82] study comparing a systemic corticosteroid group with an intralesional steroid injection with concomitant topical steroid group, the complete or partial response rates of groups were 71.9% and 93.5%, respectively. The recurrence rates of the groups were 46.9% and 8.7%, respectively. Also, the corticosteroid-related side effects were more common in patients using systemic corticosteroids. They concluded that combined steroid injection and topical steroid treatment in IGM is as effective as systemic steroid treatment and this combination can be the first-line treatment approach with rare side effects.

In conclusion, intralesional steroid injection with concomitant topical steroid application can be used easily in patients with uncomplicated IGM, due to its ease of use and good patient compliance with satisfying results.

Methotrexate

In the treatment of IGM, methotrexate was first used in the 2000s [56, 83].

Kim et al. [83] initiated corticosteroid therapy as the first-line treatment in their patients with IGM. Although the initial response to corticosteroid therapy was good, the lesions recurred with the reduction of the corticosteroid dose. For the recurred lesions, the authors administered azathioprine first. Once the patient could not tolerate azathioprine, they started methotrexate at a dose of 10 mg/week and then increased the dosage to 15 mg/week which was continued for 12 months. They did not observe any serious side effects or recurrence in the patient. Based on their experience with the initial patient, the authors used methotrexate treatment with corticosteroids in three more patients. They reported that the duration of methotrexate use varied between 3 and 6 months, but two of three patients relapsed after 1–3 months of discontinuation of the drug. They concluded that methotrexate can be used for troublesome IGM patients to avoid corticosteroid-related side effects.

Katz et al. [56] used methotrexate (10 mg/week per oral, 12 months) due to the development of corticosteroid-induced diabetes mellitus in their first IGM patient. Methotrexate (7.5 mg per oral/week) was administered in another patient as a consequence of recurrence after the reduction of corticosteroid dose.

Until now, methotrexate has mostly been used for the treatment of patients with recurring or refractory IGM. This has been at different doses and durations [12, 13,

16, 52, 67, 70, 71, 84–87]. It has also been preferred as a maintenance therapy for IGM patients in remission with corticosteroids [88]. However, recently, there have been studies proposing methotrexate as a first-line therapy [13, 85, 87]. The commonly used dosage is 10–20 mg per oral/week.

In conclusion, methotrexate is effective in patients with IGM, and with once-a-week dosage, it is an easy-to-use drug. According to recent studies, methotrexate seems to be a treatment option in IGM, especially in patients with refractory or recurrent disease. However, patients should be monitored due to possible hematological side effects especially in the treatment of coexisting rheumatologic diseases.

Azathioprine

Azathioprine, a purine analogue and an immunosuppressive drug, is also used in some rheumatologic or autoimmune diseases such as rheumatoid arthritis, granulomatosis with polyangiitis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus. There is also little experience with azathioprine for the treatment of IGM [69, 87–89]. Azathioprine is usually used in combination with corticosteroids as a maintenance therapy to avoid the side effects of corticosteroids.

The most comprehensive study with the use of azathioprine for the treatment of IGM is by Konan et al. [89]. The authors administered azathioprine at a dose of 150 mg/day with corticosteroid in 14 IGM patients. They decreased both the corticosteroid and azathioprine doses over time and the treatment period lasted for 6–24 months. As a result, they concluded that the addition of azathioprine to corticosteroid allows reduction of corticosteroid doses and may increase the success of the treatment with lower steroid-related side effects.

Mycophenolate Mofetil

In an IGM patient refractory to corticosteroid and methotrexate therapy, mycophenolate mofetil, an immunosuppressive drug that inhibits inosine monophosphate dehydrogenase, and intralesional injections of triamcinolone acetonide were used. The study emphasized the effectiveness of mycophenolate mofetil in IGM treatment [90].

In summary, in order to conclude that mycophenolate mofetil is effective in IGM treatment, further research such as reporting the use of mycophenolate mofetil as a single agent are needed.

1.1.5 Traditional Treatment

In an interesting traditional medicine study by Xue et al. [91], the efficacy of "Chuang Ling Ye," a traditional Chinese herbal medicine compound, was investigated for the treatment of IGM. The authors found a statistically significant decrease in the mass size and pain scores in IGM patients who were administered Chuang

Ling Ye. Also, the expression of interleukin-1β, interferon-γ, and tumor necrosis factor-α levels reduced in these patients.

In another interesting traditional medicine study, IGM patients were divided into two groups: patients who underwent surgery only and those who underwent surgery plus "Yanghe decoction," a traditional Chinese herbal formulation which has various anti-inflammatory effects. Yanghe decoction was applied to the patients daily, 30 minutes after breakfast and after dinner for 3 months. It has been reported that patients who were administered Yanghe decoction achieved complete remission in a shorter time, had a higher rate of complete remission, and had lower recurrence rates [92].

Yuksekdag [76] published an article about the efficacy of St. John's-wort (*Hypericum perforatum*) oil for intractable skin lesions of patients with IGM. Oil massage was recommended after the complete regression of granulomatous mass with oral steroid therapy. Although the study group is small and the oil massage was not the only treatment modality, it seems to be effective which may be due to two important constituents of St. John's-wort oil, hypericin and hyperforin, which are proven to have antimicrobial, anti-inflammatory, and antioxidant effects.

A traditional and complementary medicine treatment recommendation has been revealed by Caliskan et al. [93] by using medicinal leeches and cupping therapy on 30 patients with IGM. They stated that symptoms had completely resolved within mean 110.3 days and complete radiologic response was confirmed 3 months after the end of the therapy. There was no relapse after the follow-up period of 22 months [93].

Recently, a case report from India was published with regards to the Ayurvedic management of IGM. This study reported that Ayurveda may be an effective treatment option with significantly fewer adverse effects compared with steroids and antibiotics and it may be used in both managements of symptoms and prevention of recurrence [94].

In conclusion, more evidence-based studies are required on traditional medicine practices for the treatment of IGM.

1.1.6 Others

Colchicine

Colchicine, a well-known drug for a long time, has been used in autoimmune and inflammatory diseases. Some mechanisms of action of colchicine are the inhibition of neutrophil activation and migration to inflammation sites, while inhibiting microtubule polymerization and thus inhibiting mitosis by binding to tubulins [95]. Although colchicine is used in IGM treatment generally in combination with other immunosuppressive drugs, there has been little evidence on dosing and effectivity [63, 69, 96–98].

Etanercept

In a patient with arthritis, erythema nodosum, and IGM, an NSAID was prescribed and no response was obtained in erythema nodosum and IGM; however, little improvement was seen in the arthritis findings. High-dose corticosteroid treatment was administered to the patient, but it was reported that only erythema nodosum healed in a short time, and there was no improvement in breast findings. There was also no improvement detected with the treatment of azathioprine and danazol. Thereafter, etanercept, a tumor necrosis factor inhibitor, was given at a dose of 50 mg every 2 weeks. Following this, the etanercept dose was tapered, and methotrexate was started. The patient, who remained in remission for 6 months, relapsed and etanercept was started again. In the light of these findings, the authors concluded that etanercept may be effective for the treatment of IGM [73].

Minocycline

The anti-inflammatory and immunomodulatory activities of minocycline, a tetracycline group antibiotic, have been demonstrated in different ways [99]. In the treatment of IGM, minocycline was included in only a case report [60].

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous concentration of human platelets that contains many growth factors actively secreted by platelets as platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, and epithelial growth factor to initiate wound healing. It also contains cell adhesion molecules like fibronectin. The clinical application of PRP in sports, spine, and musculoskeletal medicine has soared in the last decade. Starting from its efficacy in these areas of medicine, we planned to use it for a patient with a refractory and recurrent IGM with multiple ulcers and fistulae. After cleaning the wound with saline, PRP was applied and dressings were checked daily and the procedure was repeated if needed. On the tenth day of treatment, an obvious recovery in the wound was achieved. It sounds to be a promising treatment option with no known side effects; however, a large number of series are required [100].

Conclusion

Despite these findings, IGM still remains a mystery. Until the etiopathogenesis is fully understood, it seems that the continuation of symptomatic treatment will be the first-line treatment. The only tool we have to guide this mysterious illness is classification schemes. The scheme below may help to classify the disease according to symptoms and suggest treatment strategies (Fig. 1).

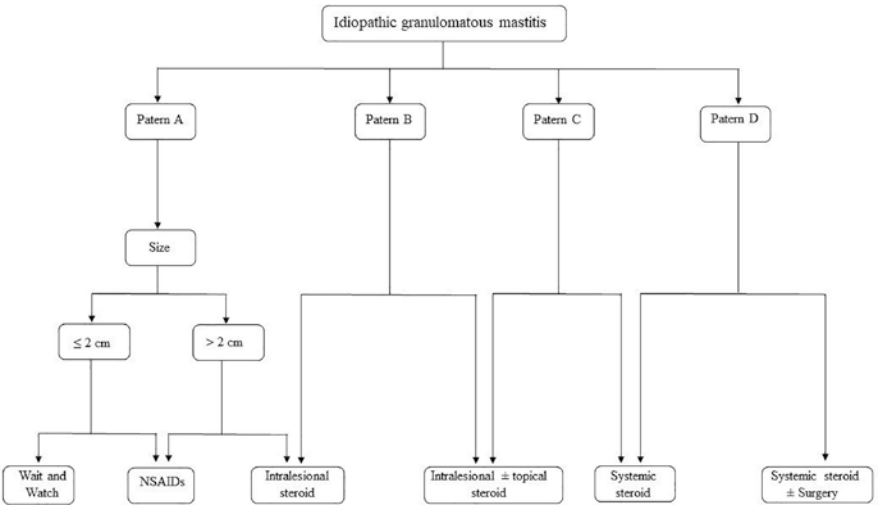

Fig. 1 An overview of treatment approaches in IGM

Treatment of IGM Patients with Erythema Nodosum

It is well known that patients with IGM may have extramammary manifestations such as erythema nodosum, arthralgia/arthritis, or episcleritis [17, 41, 101]. An ideal treatment approach has not yet been established in IGM patients with erythema nodosum, like in all IGM patients [41, 43, 45, 69, 85, 98, 102–107]. Most of the literature on this subject is in the form of case reports. Although it has been reported that different corticosteroids have been successfully used with different doses in these patients, there have been some patients who do not respond to treatment or have recurrence when the corticosteroid dose is tapered.

In the study by Akın et al. [41] which is one of the three important studies, they reported that they achieved complete response in all their patients with a relatively high dose of methylprednisolone treatment and no recurrence was observed. However, in a case report where the same drug was used at the same dose, it was reported that no response was obtained [105]. In another study comparing IGM patients with and without erythema nodosum, they reported success rates of 50% and 75%, respectively, and recurrence rates of 25% and 17.4%, respectively [45]. In the final important study on this subject, they emphasized that methotrexate treatment could be a useful option in IGM patients with systemic inflammation findings such as erythema nodosum and/or arthritis [85].

In conclusion, although there is little experience in the treatment of IGM patients with erythema nodosum, it is generally believed that corticosteroid therapy is successful. Methotrexate may be also useful in patients who do not achieve the desired success with steroids or in patients with recurrence. However, it is a fact that prospective studies are also needed.

Treatment of IGM Patients with Pregnancy

Idiopathic granulomatous mastitis is not common during pregnancy, but if it exists, it is usually diagnosed in the second or third trimester. Erythema nodosum and/or arthritis is also more common in these patients than in IGM patients who are not pregnant. The patients being pregnant at the time of diagnosis constitute 4.5% to 9% of all IGM patients [17, 24]. Literature in IGM treatment in pregnant women is very limited [48, 81, 89, 106, 108, 109]. Two approaches draw attention in pregnant IGM patients, one of them is observation, and the other is corticosteroids. Due to the possible side effects of the drugs on both the patient and the fetus, it is generally thought that medical treatment should be avoided or postponed. But antenatal corticosteroid administration is well known to prevent respiratory stress, especially at fetuses at risk of early-term labor. Therefore, systemic or local corticosteroids (intralesional administration or topical) can be an option in pregnant patients, especially in the third trimester within the knowledge of the patient's obstetrician against the risk of surrenal gland suppression in the fetus. However, this research area also requires further studies.

2 Prognosis

Idiopathic granulomatous mastitis is a benign inflammatory breast disease that is self-limited and can achieve self-remission [17, 23, 26]. Various studies have reported different recurrence rates in IGM patients, depending on the treatment approaches [11, 37, 110–112]. The overall recurrence rate independent of treatment ranges from 16.2% to 29.1% [37, 112].

In a highly comprehensive study by Kaviani et al. [37], according to treatment approaches, regarding the recurrence rates for observation, nonsteroidal anti-inflammatory drugs, corticosteroids, antibiotics, methotrexate, and surgery (open drainage, incision biopsy and open drainage, excision biopsy, and breast-conserving surgery) were 12.9%, 16.9%, 24.8%, 12.5%, 8.3%, and 48.7%, respectively.

In a meta-analysis by Godazandeh et al. [11], 559 IGM patients were included, and the overall recurrence rate was 13.2% for all patients, while this rate was 17.7% in patients who received corticosteroid therapy, 8.7% in patients who underwent surgery alone, and 3.2% in patients who had surgery and steroid therapy together.

Studies on factors affecting recurrence in IGM are limited. Azizi et al. [110] showed the only factor significantly associated with the recurrence was the presence of skin lesions on affected breasts. Çetinkaya et al. [113] found that the recurrence rate was high in patients with high neutrophil to lymphocyte ratio (>5.02). The most important limitation for this study is the low number of IGM patients, especially the ones with recurrence.

In the multicenter study by Uysal et al. [112], 750 IGM patients were reviewed. The percentages of the first recurrence and re-recurrence were 17% and 3%, respectively. They found statistical relationships between recurrence and pregnancy, breastfeeding, smoking, and history of breast infection in IGM patients.

Yilmaz et al. [75] used a scoring system that could be useful in predicting the recurrence of IGM. In this scoring system, parameters including number of births, duration of lactation, body mass index, luminal inflammation score, existence of fistula, and abscess/collection in ultrasonography were used. In this study the most important limitation is the small sample size of IGM patients with recurrence.

Idiopathic granulomatous mastitis is also a disease of secondary complications such as infection and delayed wound healing.

In conclusion, IGM is an inflammatory breast disease that can sometimes be controlled with a "wait-and-watch strategy" approach alone or sometimes with using different treatment options such as immunosuppressive drugs. For reasons unknown, this disease can remain dormant for a long period of time before recurrence. It is perhaps important to maintain long-term follow-up but no measure for prevention has been advised. However, recurrences are important complications, and more studies, especially prospective ones, are required describing appropriate and effective treatment strategies for patients with recurring IGM.

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