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Idiopathic Granulomatous Mastitis: An institutional Experience from a Referral Center

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ABSTRACT

Background: Idiopathic Granulomatous Mastitis (IGM) is a chronic inflammatory disease of the breast. Recent studies have shown an increase in its prevalence especially in developing countries. A standard for the treatment of the disease that has not been established yet. The aim of this cross-sectional study was to review the clinical characteristics and the result of treatment at Motamed Cancer Institute (MCI).

Methods: This retrospective study was conducted on 383 women who referred to Motamed Cancer Research Institute with confirmed diagnosis of IGM from March 2015 to February 2018. The demographic and clinical characteristics and the result of treatment options were extracted from the patients' medical records. The data was analyzed using SPSS, version 22.

Results: Among 383 pathologically proven patients with a mean age of 35.6 ±7.593 years, 97% had the history of pregnancy and 95.2% had breastfeeding. In response to the prescribed treatments, among 241 patients with available follow-up, the most commonly used treatment was Corticosteroids (Cs) + Methotrexate (Mtx) (70.1%), where the highest complete remission was in the group receiving Cs (100%) and Mtx (97%), respectively, and the highest partial remission belonged to Cs + Mtx at 21.3%. The shortest time to complete remission was seen in Mtx group with the mean duration of 5.83 months and the highest recurrence rate was seen in the group receiving Cs alone (16.7%).

Conclusion: According to the results of this study, among the prescribed treatments, the highest rate of complete remission with the lowest duration and recurrence rate belonged to Methotrexate regimen. Corticosteroids were associated with a high rate of complete remission and a high rate of recurrence. Implementing clinical trials regarding the best treatment options for IGM is recommended.

INTRODUCTION

Idiopathic Granulomatous Mastitis (IGM), also known as Granulomatous Mastitis and Granulomatous Lobular Mastitis, is a chronic benign disease of the breast with unknown etiology, which is mostly seen in young women with a history of pregnancy shortly after their last pregnancy. Even though most studies have reported IGM to be a rare disease, recently many studies have been published especially from developing countries, which show an increase in their prevalence.[1] The most widely cited assumption about the etiology of the disease is autoimmune or hypersensitivity reaction which involves both humoral

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and cell immunity and creates non-caseating granuloma. Although no specific antigen or infectious agents have been established, trauma to the epithelium of the mammary ducts and extravasation of milk or duct secretions to the connective tissue, hyperprolactinemia, oral contraceptives or bacterial origin have been considered.[2]

The most common signs of the disease are palpable mass, pain, inflammation and erythema, abscess formation, single or multiple fistulas, nipple retraction and breast deformity and sometimes axillary adenopathy. Regarding the imaging methods, in most cases it is classified as a differential diagnosis for breast cancer and the definite diagnosis is only through histological evaluation.[3,37] Although some studies recommend surgical excision or incision and drainage, others recommend medical treatments such as antibiotics, corticosteroids, immunosuppressives, anti-inflammatory medications and sometimes only observation of the patient without any treatment. Nevertheless, the most appropriate treatment protocol is yet to be identified.[4]

Considering different reports from Asian countries showing an increase in the prevalence of this disease and challenges in the treatment, this study was designed to report the identified cases of IGM who referred to MCI as a referral center for breast diseases in Iran, in a period of two years between March 2015 and February 2018.

METHODS

In this cross-sectional study, all the patients who referred to Motamed Cancer Institute with confirmed diagnosis of IGM between March 2015 and February 2018 were reviewed. The patients' demographic and clinical characteristics were extracted from their medical records. In cases with no information about outcome, follow up was done through phone calls or invitation to the clinic. Some patients visited MCI only once and follow-up was not possible. So only their demographic and clinical characteristics were analyzed statistically. Regarding the treatment protocol of MCI (unpublished), antibiotic therapy and drainage or aspiration of purulent discharge were part of the palliative treatment and were not considered as treatment options. In terms of severity of the disease, patients were divided into three categories according to the standards of the previous studies.[5] Mild severity: size<2cm, without fistula to the skin and with slight pain, Moderate severity: Size 2-5cm with accumulation of pus, one fistula and little discharge, and Severe disease: size>5cm, severe pain, multiple fistulas and wound with more than 20cc of discharge. All cases were examined for Tuberculosis (Ziehl–Neelsen staining) and fungi (PAS) to rule out these origins. The prescribed medical treatments were Corticosteroid (C) (prednisone 0.5-1mg/Kg or Dexamethasone 0.5-1mg), Methotrexate (MTX) alone 10-20mg weekly, C plus MTX, or mixed treatment containing Azathioprine (AZA) 25-50mg daily. In terms of response to the treatment, they were also divided into three categories. Complete remission: lack of pain, mass or new fistula. Partial remission: less pain, shrinkage of previous lesions, decrease in the number of fistulas (it is possible that some of the previous lesions turn into fistulas and have discharge), no response to the treatment or disease progression: formation of new masses, enlargement of the existing masses, erythema at the site of the previous masses with fistula formation, and recurrence: after complete remission, formation of a new mass, enlargement and erythema of previous masses, formation of a new fistula and contralateral breast involvement.

Methods of analysis

Using SPSS software version 22, absolute and relative frequency distribution of data were determined according to the contextual variables (demographic and clinical). Student t-test was used to compare the distribution of quantitative variables and chi-square test was used for qualitative variables.

This study was approved by the scientific council of Motamed Cancer Institute and ethics committee approval #IR.ACECR.IBCRC.REC.1399.002 was obtained from Motamed ethics committee in May 2020.

RESULTS

Overall, among the patients referring to MCI from the March 2015 to February 2018, 382 patients with the diagnosis of IGM were included. The mean age of the patients was 35.6±7.685 (20-70) and the median age was 34. Forty eight percent had right breast involvement, 49% had left breast involvement and in 3% of cases symptoms were bilateral. The demographic characteristics of patients are shown in Table 1.

All of the patients had histologic diagnosis for IGM. The most common symptoms were mass, pain, fistula, inflammation and erythema, respectively. Most patients referred with a combination of these symptoms. This information is shown in Table 2.

Given the most common proposed risk factors and underlying diseases for IGM, the frequency of the underlying diseases in the medical records is shown in Table 3.

In some cases, the patients had multiple accompanying diseases. Since MCI is a referral center for IGM, many of the patients were referred to this center after long-term antibiotic consumption.

Table 1. The demographic characteristics of patients with definite diagnosis of IGM

Variable	N	%	Mean±SD
Age (years)	382		35.6±7.685
Number of full-term pregnancies	363		1.9±1.192
Duration of breastfeeding (months)	356		36.3±26.330
Duration of OCP use (months)	96		45.6±49.860
Menstrual status			
Pre-menopausal	346	91.1	
Pregnant	6	1.5	
Lactating	9	2.4	
Post-menopausal	19	5	
Marital status	340		
Single	9	2.4	
Married/widowed/ divorced	345	97.6	
History of abortion			
Yes	84	28.3	
No	274	71.7	
History of breastfeeding			
Yes	317	95.2	
No	16	4.8	
History of OCP use			
Yes	100	27.9	
No	259	72.1	
History of smoking			
Yes	39	10.8	
No	321	89.2	

Table 2. Clinical characteristics of the patients with IGM

Symptom	N	%
Mass	311	81.4
Pain	134	35
Fistula	115	30.1
Erythema/edema/inflammation	123	30.4
Abscess	19	5
Ulcer (scar of previous fistula)	5	6.4
Breast deformity/ nipple retraction	27	7.5

Regarding the possible response to the treatments, after starting medical treatment, 141 patients did not refer again and their outcome was unknown. . Consequently, in the rest of the analysis 241 patients were included. According to the prescribed medical treatments, the patients were divided into four groups as mentioned in the materials and methods section. Consequently, in the rest of the analysis 241 patients were included.

Initially, 10% of the patients received C regimen, 13.7% MTX, 72.2% C+MTX and 4.5% AZA. Due to the remission and flare up nature of IGM, the patients might shift from one regimen to another during the treatment. The results of the treatment at the end of the study according to the treatment regimen are shown in Table 4.

Overall, 82.2% of patients experienced complete remission and 17.8% showed partial remission at the end of the study. The mean duration to complete remission was 18.2 months (3-85 months) without considering the severity of the disease and for partial remission (follow-up till the end of the study) was 18.9 months (4-53 months).

Table 3. Frequency of the accompanying diseases in the patients (N=357)

Underlying disease	N	%
Hyperthyroidism	10	2.8
Hypothyroidism	32	8.4
Diabetes	19	4.5
Psychological diseases	14	4.7
Pituitary adenoma	4	1.04
Autoimmune disease	2	0.3
Cardiopulmonary disease	7	1.7
Hypercholesterolemia	6	1.7
Obesity	5	1.4
Breast biopsy	30	1.1
Without underlying disease	259	72.5
Total No	357	100

Table 4. Comparison of responses to the treatment based on the treatment regimen

Variables	Patients (at the beginning of the study)	Patients (at the end of the study)	Complete remission		Partial remission	
Treatment regimen	N	N	N	%	N	%
Corticosteroids	24	8	8	100	0	0
Methotrexate	33	30	29	96.7	1	3.3
Corticosteroids+ Methotrexate	174	169	133	78.7	36	21.3
Azathioprine-containing regimen	10	34	28	82.4	2	17.6
Total	241	241	198	82.2	43	17.8

Comparing the treatment regimens in terms of complete and partial remission, the shortest duration was observed in the group receiving Methotrexate. The average duration of complete and partial remission is shown in Table 5.

During the study, 40 patients (17.9%) experienced recurrence after a period of complete remission to treatment. The distribution of these patients in relation to medical regimen is shown in Table 6.

The highest rate of recurrence was seen in C (16.7%) and C+M (14.4%) groups.

In terms of severity, 16.9% referred with a mild disease, 43.3% moderate and 39.7% with severe disease

Table 5. Duration of treatment response based on the treatment regimen

Treatment regimen	N	Complete remission Mean duration (Mo) Min-Max	Partial remission Mean duration (Mo) Min-Max
Corticosteroids	8	12.4± (7.652) 3-24	
Methotrexate	30	5.8± (7.714) 3-38	4
Corticosteroids+ Methotrexate	169	18.8±11.844 3-64	18.6±12.339 5-35
Azathioprine containing regimen	34	29.2±17.877 3-85	23.5±10.877 6-37

Table 6. Frequency of recurrence after response to the treatment in each group of treatment

Treatment regimen	N at the beginning of the study	N of recurrence	% in the treatment regimen group
Corticosteroids	24	4	16.7
Methotrexate	33	2	6.1
Corticosteroids + Methotrexate	174	25	14.4
Total	231	31	13.4

DISCUSSION

The results of this cross-sectional study at Motamed Cancer Institute showed that IGM is not a rare disease in Iran like other reports from Asian countries. The mean age of patients was 35.6, 92% had a history of pregnancy and childbirth and 90% had a history of breastfeeding. In terms of severity, 22.6% had mild, 28.2% moderate and 49.1% severe symptoms. Among the prescribed therapeutic regimens, the most common one was Corticosteroids + Methotrexate with the frequency of 70%. The highest rate of complete remission was seen in Corticosteroid group (100%) with the mean duration of 12.4mo and Methotrexate group (97%) with the mean duration of 5.8 months. Recurrence after complete remission was seen with the highest frequency (16.7%) in the Corticosteroids group.

Even six decades after the first reports of IGM, this disease is still challenging for specialists and poses cosmetic problems for patients. Lack of knowledge in this field makes surgical manipulation a therapeutic option, while surgery is associated with a high rate of recurrence and tissue distortion and even recurrence after mastectomy.[6] For the first time in 1972 Kessler *et al*. reported 5 cases of mastitis whose pathology was different from the previously reported types. All of these patients were in their child-bearing age (27-40 years) and were affected in the period of 1.5 to 5 years after their last pregnancy. Due to similarities with malignant lesions, all these patients underwent surgery and two of them received radiotherapy. These authors emphasized that IGM is different from plasma cell mastitis, fat necrosis, and tuberculosis mastitis, and due to the similarities in pathologic findings with Granulomatous Orchitis and granulomatous Thyroiditis, it could have an autoimmune origin.[7]

In 1979, Brown *et al*. reported two similar cases and raised the hypothesis of local immunologic reaction to breastfeeding.[8] Similar cases were also reported by Cohen in 1977,[9] Murthy in 1973,[10] and Koelmeyer in 1976.[11] Most of these studies were limited to case reports and the number of these reports has increased recently especially from Asian countries.[12,13]

Although various predisposing factors have been mentioned for IGM, none of them have been proven. In this regard, the most common hypotheses are autoimmune, infectious and Hormonal factors.[1] Especially in cases with arthritis and skin lesions like erythema nodusom, high concentrations of lymphocytes in the tissue, and appropriate response to immunosuppressive treatments, the autoimmune hypothesis is considered.[14] Based on this hypothesis, there is an inflammatory response to the damage of the mammary ducts epithelium which can occur following the penetration of the secretions into the interstitial tissue.[15] There are other theories like high levels of serum prolactin which can cause ductal obstruction with milk. Nevertheless, routine prolactin test is not recommended in the diagnosis of IGM.[16] The infectious origin has few documents although some cases of association of IGM with tuberculosis or Corynebacterium infections have been reported.[17,18] Other risk factors are race,[19] smoking,[20] and alpha-1 antitrypsin deficiency.[5] In our study, none of the probable risk factors were common except for the history of breastfeeding seen in 95% of the patients with the average duration of 36 months. The mean age of the patients in our study was 35 years. Most observations are in favor of the fact that this disease mostly involves women in the age range of 32-37 who have at least had one pregnancy and breastfeeding. In the study of Kaviani *et al*., the mean age was 34.06 years,[5] and Sheybani *et al.* reported the mean age of 32.8 years.[15]

In terms of clinical symptoms, the most common ones in our study were palpable mass 81%, pain 35%, fistula 30%, inflammation 30.3%, and abscess 5%, respectively. Also, according to other reports, the most common symptom is painful palpable mass that can be associated with erythema and inflammation. It commonly appears with multiple peripheral or rare central abscesses, sinus or fistula to the skin, nipple retraction and axillary adenopathy.[21]

Due to non-specific symptoms, the disease can usually take months from the onset of the symptoms to the time of the diagnosis. Mammographic or sonographic signs are usually not pathognomonic. Hypo-echo tubular lesions, multiple abscesses, Hypo-echo lobular mass, tissue distortion, fistula to the skin, and axillary adenopathy can be seen in sonography. Mammographic findings consist of focal asymmetry, diffused hyper-density, mass, retraction, and tissue heterogeneity, similar to cancer.[22,23]

Biopsy is the Gold Standard in diagnosis of IGM which is better taken with a core needle. The sensitivity of CNB in diagnosis is 96% while it is 21% for FNA.[24] In the pathologic samples, granulomatous lesions without necrosis are accompanied by giant cell infiltration, histiocyte, lymphocyte and plasma cells seen in the center of the breast lobules. The affected parenchyma usually loses its acinar structure and the ducts are damaged.[25] The tissue sample should be examined for acid fast bacilli and fungi.[26,27] In our study, all cases were examined for tuberculosis and fungi but the results were negative. Other differential diagnosis included sarcoidosis, Wagner granulomatosis, histoplasmosis, actinomycosis, foreign body granuloma, fat necrosis and especially inflammatory breast cancer.[28]

Irrespective of etiology, the most important challenge of IGM is the choice of treatment ranging from palliative care and monitoring to medical treatment, surgery and even mastectomy.[29] The treatment of these patients usually takes a long time, requiring frequent visits to assess the response to the treatment, change treatment options and doses, or start a combination therapy. In our study, FNA of the secretions was done in cases of abscess formation. Oral antibiotics were recommended for a short period up to two weeks only in cases suspected of bacterial infection. Antibiotic therapy alone is not usually recommended in such studies except for a short time (7-10 days). NSAIDs was not used as a treatment regimen. These palliative treatments were used uniformly for patients if needed. According to the main treatment, the patients were divided into four groups consisted of Corticosteroids+Methotrexate (C+MTX), Methotrexate alone (MTX), Corticosteroids alone (C) and Azathioprine containing regimen (AZA). At the start of the treatment, 10% of the patients received C regimen, 13.7% MTX, 72.2% C+MTX, and 4.5% AZA. However, at the end of the study, regarding the response to the treatment and the severity of the symptoms, they were changed. In total, 82.2% had complete remission, 17.8% partial remission, and 13.4% experienced recurrence after complete remission. The highest rate of response was for C group (100%) with the mean duration of 12.4 months and the highest rate of recurrence. Methotrexate showed the highest rate of complete remission (97%) in the shortest time (5.8mo).

Among Iranian studies, Kaviani *et al*. reported complete remission in 48.6% of the patients, no response to the treatment in 6%, partial remission in 16.8%, and recurrence in 29.1%. According to this study, the best results were obtained for follow-up without treatment which led to 44% complete remission, followed by Methotrexate which showed the second best results. The response to the treatment with NSAIDs was acceptable, although it was used in mild and moderate cases. The highest recurrence rate was seen after discontinuation of Prednisolone (24.8%) and after surgical intervention (48.7%). They concluded that in moderate to severe cases, NSAIDs have a similar effect as Prednisolone with less side

effects, and due to the benign nature of the disease, they recommended less invasive treatments.[5] However, as the results of this study showed, in case of treatment with NSAIDs after 17.5 weeks, only 31% of the patients showed complete remission and 16.9% had recurrence after discontinuation of the medication.

Studies on the conservative treatment of IGM are limited, and severity has not been specified, with many studies only focusing on breast deformity and impaired quality of life among the patients. In our study, in terms of severity, 16.9% of the patients referred with a mild disease, 43.3% with a moderate disease and 39.7% with a severe disease. Therefore, most of the patients referred while at moderate to severe stages that required more than just conservative treatment. The recurrence rate for patients who have only been monitored has been reported to be 50%.[38] Yukawa *et al.*, in their report of 13 patients, only used deep drainage of the pus and followed them between 4-28 months. They believed that this option was shorter than the duration of using corticosteroids.[30] Bouton *et al*. reported 27 patients with IGM and showed that they improved after an average duration of 7.4 months without treatment.[31]

Treatment with corticosteroids was first proposed by Herthogh *et al*. with 30mg daily for two months which reduced the size of the lesion but had side effects including weight gain, diabetes and Cushing's syndrome.[32] Although Glucocorticosteroids are the first line of treatment in most studies, recurrence rate and side effects are high with these drugs.[15,33] In our study, Corticosteroids were initiated in 24 patients, continued in only eight patients with complete remission of 100 % and 17.4% recurrence rate. The patients who had partial or no response to the Corticosteroids were shifted to another treatment regimen.

Keller *et al.* used 1mg/kg daily for 2 to 6 months and only 15% recurrence was reported in this group.[34] Wolfrum *et al.* recommended Prednisolone 30mg twice daily for two weeks and then gradual tapering based on the symptoms with a visit at two weeks interval to assess the response to the treatment and the incidence of complications. This group had 90% complete remission to the treatment and 16% had recurrence.[16] Overall, it seems that oral corticosteroids with complete dose is a suitable primary option for IGM patients; however, recurrence after tapering could occur which would necessitate gradual tapering and combination therapy. Methotrexate has been highly recommended in previous research, in cases where corticosteroids failed or was accompanied with complications. The recommended dose is 7.5 to 25mg weekly in combination with Folic Acid daily or weekly.[32] The most common complications are Stomatitis, Leukopenia, abdominal pain, exhaustion, fever and chills, dizziness, and infection.[13]

In our study, 33 patients (13.7%) only received Methotrexate with 97% complete remission after 5.8 months and 3% partial remission within 4 months of follow-up. Recurrence rate was 6.1%. In the study of Postolova *et al*., 19 patients with IGM diagnosis who had failed treatments received Methotrexate 10-15mg weekly which increased to 20-25mg. In a period of 6 months, symptoms improved in 94.4% and 22.2% had complete remission. After 15 months of treatment, 75% of the patients had complete remission. The average duration of treatment was 13-15 months. Only one patient did not respond to the treatment and went through mastectomy.[13]

Sheybani *et al*. treated 28 patients with IGM. The average duration of follow-up was 12 months (6-22). In 15 patients (68.2%), the primary treatment was Prednisolone 1mg/kg, six patients received Prednisolone in combination with Methotrexate (7.5-10mg weekly) and one patient received only MTX. From the 15 patients who received Prednisolone, 10 patients had complete remission (66.6%) and for the 5 other cases, Methotrexate was started due to the recurrence of the disease or the complications of the Corticosteroids. In total, 12 patients (54.5%) received MTX as the first line of treatment or to reduce the dose of Corticosteroids. The rate of complete remission to the treatment in this study was 72.7%. These researchers recommended Corticosteroids as the first line and MTX to taper Corticosteroids and decrease its complications or in cases of resistance to treatment.[15]

Akbulut *et al*. reviewed 84 studies in the period of 1972-2010 on 537 patients. The complete remission rate in the patients receiving Steroids was 72.2% and recurrence rate was 20.3%. Response to the treatment in the MTX group, which was usually prescribed after recurrence or when there was no response to Steroids, was 83.3% and recurrence was 16.7% which led to mastectomy. This study recommended Palliative treatment or Corticosteroids in mild and localized form, but in cases of resistance to Corticosteroids or the complications of them, MTX was recommended.[32]

Finally, the use of surgery in IGM treatment has been reported from incision and abscess drainage to extensive excision and even mastectomy.[35] Some studies are in favor of this treatment,[20] and some are against it and limit the indication for surgery in cases resistant to all treatments.[36] This opposition is due to severe complications and the high rate of recurrence up to 50%.[29] None of our patients underwent excisional surgery or open drainage of abscess.

The most important limitations of this study were a wide range of severity rates of the disease among the patients, a long time of using previous treatments, lack of access to some patients for follow-up and the

necessity of combination therapy in IGM, which are common limitations in retrospective studies. These limitations raise the need for prospective studies and especially clinical trials.

CONCLUSION

According to the results of this study, among the studied medical treatments, the highest rate of complete remission with lowest duration and recurrence rate belongs to Methotrexate regimen. Corticosteroids alone was associated with a high rate of complete remission but a high rate of recurrence. Given the autoimmune nature of IGM, such results are justified. Methotrexate could be recommended especially in moderate to severe forms and as an additional treatment to taper Corticosteroids. The implementation of clinical trials regarding the best treatment options for IGM is recommended.

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CONFLICT OF INTEREST

None.

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