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EFFECTIVENESS OF METHOTREXATE IN THE TREATMENT OF GRANULOMATOUS MASTITIS

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ABSTRACT

Background: Granulomatous mastitis is an uncommon, benign inflammatory disease of the breast. Clinically and radiologically, granulomatous mastitis can mimic a tumor. Various treatment modalities are available in clinical practice including medical and surgical interventions. **Aim of the study:** To assess the efficacy of the use of combined therapy of methotrexate and steroids in the management of granulomatous mastitis in whom steroid monotherapy failed or poorly responded. **Patients and methods:** For this retrospective study, data from 19 patients with biopsy-proven granulomatous mastitis were assessed. Demographic features clinical characteristics and course of the patients were obtained from medical records. **Results:** Following 3-month methotrexate therapy, 12 patients showed (63.2%) complete, 4 patients (21.1%) partial response, and the treatment had no effect in 3 patients (15.8%). No adverse effect was documented because of the methotrexate therapy. **Conclusions:** combination therapy of methotrexate and steroids in patients not responding to steroid monotherapy or having adverse effects should be regarded as alternative therapy instead of surgical treatment.

KEYWORDS: Granulomatous Mastitis, Methotrexate, Steroid.

INTRODUCTION

Granulomatous mastitis (GM) is a benign and chronic inflammatory disease of the breast that was first reported by Kessler and Wolloch in 1972.[1] This uncommon entity usually affects female patients during their child-bearing period.[2] GM is histologically characterized by a non-caseating granulomatous inflammation in close proximity to the mammary lobules and ducts with multinucleate giant cells and micro abscess formation but without necrosis.[3,4]

The estimated incidence of IGM is 2.4 per 100,000 women, with a higher incidence in some Middle Eastern countries such as Iran and Turkey.[5,6]

The granulomas are usually unilateral and appear as a solid mass in the upper outer quadrant of the breast.[7] Bilateral involvement is rare. In the study conducted by Velidedeoglu et al.,[8] a series of 10 patients with bilateral granulomatous mastitis were reported for the first time.

Various clinical findings, including painfully palpable masses, fistulae, nipple retraction, breast skin inflammation, ulcers, and abscess formation have been associated with GM.[9,10]

The exact etiology of GM remains unclear, which may lead to misdiagnosis and complicate treatment.[11] Heredity, bacterial infection, fungal infection, use of contraceptive drugs, hyperprolactinemia, alpha-1 antitrypsin deficiency, and smoking are Some factors that have been blamed for causing GM. In addition, triggering autoimmune reactions due to the existence of milk proteins in the interstitial breast tissues is considered as an accepted hypothesis regarding the occurrence of GM.[12]

GM can broadly be classified into two subtypes; idiopathic and specific. Gestation, oral contraceptive

drugs, diabetes mellitus, smoking, and autoimmunity are considered the major etiological factors of idiopathic GM. Specific GM is due to foreign body reaction, sarcoidosis, vasculitis, and infectious causes such as tuberculosis, cat scratch disease, fungal inflammation, and corynebacteria infection.[9,13]

Despite a strong correlation between IGM and history of lactation and pregnancy, its occurrence during pregnancy or breastfeeding is uncommon but has been recorded.[14]

Rare cases of IGM have been reported among nulliparous women in whom hyperprolactinemia, either due to medications or pituitary tumors, was blamed to be a cause.[15]

Although no mammographic characteristics exist specific for IGM these lesions most often present as a unilateral focal or regional asymmetry.[16] In some patients, these lesions can be mammographically occult.[17] The sonographic features of IGM include lobulated, heterogeneous, hypoechoic masses with indistinct, irregular, or angular margins with posterior acoustic enhancement.[18] A wide array of approaches exists in the treatment of GM, including observation alone[19], short courses of antibiotics, long courses of immunosuppressants[20], and surgical interventions.[21] This study aims to assess the efficacy of methotrexate therapy in the management of granulomatous mastitis in which the steroid therapy alone did not have satisfactory therapeutic yield.

PATIENTS AND METHODS

This retrospective analysis was performed in various breast centers of Sulaymaniyah and Erbil governorates between July 2022 to June 2024. A sum of 19 female patients, those who were already diagnosed with GM after physical examination and histopathological assessment of samples from breast biopsies were included in the study.

Data Collection

Informed consent was taken from every hospital and health institution from where patient data were collected and the clinical data and demographic features were retrospectively attained from patients' medical records. Applied treatment options (steroids, immunosuppression, and surgical management), the duration of therapy, course, and outcomes of treatment for each patient were examined.

Improvement of at least 50% in clinical and sonographic findings at the 3rd or 6th-month follow-up visit was recognized as partial remission. While complete recovery in clinical and sonographic findings at the 6th month was regarded as complete remission. Female patients with biopsy-proven granulomatous mastitis were included in this study while other benign, malignant breast lesions, and other granulomatous diseases were excluded.

Patient assessment

All patients' data collected in questionnaire form:

—Demographic characteristics of participants

—History taking and clinical examination: general look and local examination.

—Laboratory investigations: core cute biopsy.

— Imaging techniques: bilateral breast and axillary US

Treatment

Patients diagnosed with IGM were treated with systemic steroids (40 mg/day prednisone for 3-6 months). Methotrexate treatment (5 mg/week) was added to the treatment and the prednisolone dose was reduced to 10 mg/day when we had partial or no remission or had adverse effects.

Statistical analysis

The data of patients were analyzed by application of Microsoft Excel program and Statistical Package for Social Sciences (SPSS) version 27. The outcomes of the analysis were arranged in continuous variables and categorical variables.

RESULTS

All patients included in the study were females in their reproductive age. The mean age was 36.8 years, none of whom were pregnant nor lactating at the time of clinical presentation. Demographic variables of patients regarding the duration of clinical symptoms, number of pregnancies, duration of lactation, and cigarette smoking are placed in Table.(1)

Table 1: Demographic Variables of The Study Population.

		No. (%); n=19
Symptom duration, months	1-6	12(63.2)
	>6	7(36.8)
Number of pregnancies	1-4	12(63.2)
	More than 4	7(36.8)
Lactation history	Yes	18(94.7)
	No	1(5.3)
Duration of breastfeeding, years	1-4	14(73.7)
	≥ 4	5(26.3)
Smoking	Yes	2(10.5)
	No	17(89.5)

Use of OCP	Yes	7(36.8)
	No	12(63.2)
Trauma history	Yes	1(5.3)
	No	18(94.7)

Patients were presented to various general surgery clinics and breast centers with complaints such as pain 6(31.6%), mass 8(42.1%), and combination 5(26.3 %). Through physical and sonographic examination, it was revealed that in 18 patients the lesion was unilateral, 11 patients had lesions on the left breast, and 7 on the right side. One patient had bilateral involvement. Complications were documented in 4 patients, two had erythema, and 2 developed fistulae. All patients have undergone ultrasound scanning regardless of the age of the patients. The location of the mass was noted predominantly to be on the upper outer quadrant 11(57.9%). Reactive axillary lymphadenopathy was seen in 11 patients (58.9%). Imaging modalities such as mammography were used for more detailed information about the mass and applied for patients≥ 40 years old. The mass was categorized according to BIRADS classification and categories 3 and 4 were recognized. Tissue sampling of the mass was carried out through core-cut biopsy (14 patients) and excisional biopsy of the mass wall following the drainage procedure (5 patients). The clinical presentation of the patients is shown in Table (2).

Table (2): Clinical presentation of the patients.

		No.(%); n=19
Initial presentation	Pain	6(31.6)
	Mass	8(42.1)
	Combination	5(26.3)
Breast side involvement	Left	11(57.9)
	bilateral	1(5.3)
	Right	7(31.6)
Quadrant	Upper outer	11(57.9)
	Lower outer	0(0)
	Upper inner	0(0)
	Lower inner	3(15.8)
	Retro areolar	5(26.3)
Ultrasound	Yes	0(0)
	No	19(100)
BIRAD	3	12(63.2)
	4	7(36.8)
Biopsy	core cut	14(73.7)
	drainage plus incisional biopsy	5(26.3)

Systemic prednisolone was given at 40mg/day as initial first-line therapy. An increase in serum glucose level was noted in 2 diabetic patients. In 13 patients the desired complete remission was lacking and had only partial response. Prednisone therapy did not produce any effect in 4 patients. For these reasons, the dose of steroid was reduced to 10mg/day, and 5mg/week of oral methotrexate was added to the regimen. After receiving MTX, 12 patients experienced complete remission. Partial response was noticed in 4 patients where the residual lump was surgically removed with surrounding healthy tissues. Methotrexate therapy was ineffective in 4 patients and did not show any response. In this circumstance, the mass along with normal adjacent tissue was removed by surgical intervention. The treatment methods and outcomes are shown in Table (3).

Table (3): Treatment procedures and results.

		No.(%); n=19
Duration of steroid therapy	Less than 6 month	19(100)
	More than 6 month	0(0)
Response to steroid	No response	3(15.8)
	Partial	14(73.7)
	Side effect	2(10.5)
Duration of MTX	3 month	19(100)
Response to MTX	No response	3(15.8)
	Partial	4(21.1)
	Complete	12(63.2)

DISCUSSION

GM is an uncommon benign progressive inflammatory breast disease that frequently mimics breast carcinoma clinically. Therefore, the diagnosis should be based on the findings of histological investigations and not merely on clinical presentation or radiological appearance.[22,23]

Numerous etiological theories have been proposed in the literature.[24,25] The most accepted one is autoimmunity[26] Since it is supported by three crucial facts: the favorable response to steroids and immunosuppressive drugs, with considerable remission in patients who had recurrence after surgical excision, and the predominance of T-lymphocytes demonstrated by histochemical investigations.[27]

IGM typically affects younger parous females at an average age of 35 and seldom affects men.[28,29] Every female patient in this research was parous and breasted her child for a minimum of one year.[30-32]

Smoking is thought to be a contributing factor to the damage progressing bilaterally and delaying the process of healing. Yet no conclusive association has been proven between IGM and cigarette smoking.[8] Only 2 patients (10.5%) were documented to be smokers.

The use of oral contraceptive pills (OCP) is seen by many authors to correlate with the occurrence of IGM, however, this association is still debated as there were cases reported in males and nulliparous women, in addition to reported cases with no history of OCP use, like most of our study patients.[27]

The majority of patients report slow-onset and gradually enlarging lump with or without pain which was the most alarming symptom. Signs of both acute inflammation (erythema, abscess, etc.) and chronic inflammation (fistula, orange peel appearance, nipple retraction, etc.) are usually reported complaints on admission.[33-35]

Among imaging modalities, USG and MG were utilized for appropriate patients. Determined masses are primarily unilateral. Bilateral breast involvement is noted to be rare, in accordance with literature.[36] In 18 out of 19 of our patients, the lesion was unilateral, the most affected breast was left side (57.9%), and only 1 patient had bilateral involvement.[37,38] There is no definite location of the lump on the breast, whereas Boufettal and colleagues.[29] showed that the upper outer quadrant is the most common location affected comparable with our findings.(57.9%). Ipsilateral reactive lymphadenopathy may be associated with the mass. Gautier et al. showed axillary node occurrence as 61%, it was 18% in the research by Aghajanzadeh et al.[14] Axillary lymph node involvement in our analysis was 52.63% all located on the same side.

Every patient underwent categorization on mammography or ultrasonography using the Breast Imaging Reporting and Data System (BIRADS). Our analysis included BI-RADS categories 3 and 4. Diagnosis can merely be established by ruling out other causes of granulomatous breast disorders through histopathological analysis. Core-cut and incisional biopsies are employed for tissue sampling. When there is an abscess incisional biopsy during drainage is a favorable option that was performed in our study in 5 patients. core-cut biopsy was applied in other patients.

Other etiologies of granulomatous mastitis were ruled out. In IGM the treatment process is complex and challenging and significantly lowers the quality of life. Reasons include fistulas, breast abscesses, ulcers, relapse, and chronicity.[33] Clinical and radiological pictures simulate primary breast carcinoma which raises the psychological stress of the treatment procedure.[39,40] Thus, early detection and appropriate treatment are of paramount importance.[41] Although various strategies have been documented to date, there is no unanimity on how to treat IGM.

Medical treatments, such as antibiotics, immunosuppressive drugs prolactin inhibitors, and wide surgical excision, are still in use. Though cultures for IGM are mostly sterile, antibiotics were shown to be efficacious in some research.[42,43] Whereas some authors suggested surgical excision due to more rapid healing and ultimate cure, researchers are signifying poor wound healing, fistula formation, and local relapse due to surgical procedures.[33,38] Because of their high efficacy rate, immunosuppressive-based medications were preferred as a first-line treatment over surgical treatment procedures.[42,44]

In 1980, DeHertogh et al[45] used a high dose of 60 mg/day for the first time in IGM patients and described a definite cure within 3 weeks of therapy. Akahane and colleagues[32] treated ten IGM patients using a median dose of 30 mg/day prednisolone for 5 months and achieved full remission without having surgery.[32] Altintoprak and others[25] used topical steroids for 15 weeks in therapy and reported a success rate of more than 90% after 37 months of monitoring. Researches are demonstrating that combined surgical removal with steroid therapy following downsizing mass and disappearance of abscess is the best strategy to treat IGM.[45,46]

Some individuals developed adverse effects such as hyperglycemia, moon face, and acne when receiving systemic steroid medication. In these cases, the researchers lowered the dose of steroids and/or carried out a surgical resection of the lump[41,46] Prolactin inhibitors were also employed in the medical treatment of IGM, but with no satisfactory outcome that is why they did not gain widespread acceptance. Schmajuk et al[47] treated 2 IGM patients with MTX monotherapy who were refractory to steroid therapy and were given 15 mg/week MTX in conjunction with folic acid for 6

weeks, and within one year, there were no lump, redness, or fistula. Joseph et al. pointed out that they had success over 80% through the steroid and MTX combination. likewise, Aghajanzadeh and others[14] investigated the steroid+MTX combination and observed a therapeutic success rate of 71.4%. Akbulut et al.[24] studied a case series from various clinics in a literature review and described that the remission ratio with combined steroid + MTX therapy was 83%.

In our study patients were given a low-dose 5 mg/week MTX in combination with 8 mg/day prednisone for 3 months due to steroid resistance, partial cure, and side effects of prednisone. In our study 19 female patients were recruited and 5mg/week MTX in conjunction with 10 mg/day prednisone was administered for 3 months because of incomplete remission, resistance to steroids, and prednisone adverse effects.

Complete recovery was observed in 12 patients (63.2%) after combined therapy. Partial remission was noted in 4 patients (21.1%), and the remaining mass was excised with surrounding healthy tissues by surgical intervention. Three patients (15.8%) had no response to MTX therapy. No adverse effects were noted due to the combined MTX+ steroid therapy in our analysis.

Limitation: Our study has some limitations; it is a retrospective analysis; the sample size is small given the disease is uncommon and the follow-up period was short. Conclusions: combination therapy of MTX and steroid in patients not responding to steroid monotherapy or having adverse effects should be regarded as alternative therapy instead of surgical treatment

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