Methotrexate in the Treatment of Idiopathic Granulomatous Mastitis

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Objective: Idiopathic granulomatous mastitis (IGM) is a disfiguring inflammatory breast disease without effective treatment. We report the largest IGM cohort treated with methotrexate monotherapy.

Methods: Chart review was performed on patients evaluated by the Rheumatology Clinic, with histopathologically-established IGM, treated with methotrexate, and at least one follow up appointment.

Results: Nineteen female patients with an mean age of 33.5 years were identified. Most failed treatment with antibiotics, prednisone, and surgical intervention. By 15 months of treatment with methotrexate, 94% had disease improvement and 75% achieved disease remission.

Conclusion: Methotrexate monotherapy is an effective treatment for IGM.

Introduction

Idiopathic granulomatous mastitis (IGM) is a disfiguring inflammatory disease of the breast. It commonly presents as a unilateral, tender, breast mass or localized induration with surrounding inflammatory changes and discomfort (1,2,3). Compared to Western Caucasian populations, (UK, USA, New Zealand), disease rates are higher among Middle Eastern (Egypt, Turkey, Iran) and Hispanic populations (1,4,5). In 2006, a Pakistani study cited an incidence of 0.37% while an American group reported a prevalence of 2.4 per 100,000 women (3). These rates may not be accurate as, due to increasing incidence or awareness and diagnosis, there has been an abundance of cases of IGM reported in the literature in the past decade.

Patients initially present to primary care, gynecology, or the emergency room. Evaluation includes imaging with mammography, ultrasound, and magnetic resonance imaging (MRI) with the intent of ruling out malignancy or other pathologies (2,3,6,7). Diagnosis can be made with fine needle aspiration (FNA), core needle, incisional or excisional biopsy. Typical histologic findings consist of non-caseating epithelioid and multinucleated giant cell granulomas centered on the mammary lobules. The cystic neutrophilic granulomatous mastitis pattern [or variant] (CNGM) has micro-abscesses and/or cystic vacuoles rimmed by neutrophils in the center (4,8). The underlying cause of these findings remains elusive, although corynebacteria have been identified in CNGM. Autoimmune disease, infection and hormonal disruption have all been proposed as etiologies for IGM (5). An autoimmune pathogenesis is favored given the inflammatory milieu of neutrophils, lymphocytes, and plasma cells and the treatment response to glucocorticoids and methotrexate (4,5,7). Other causes of granulomatous lesions must be

excluded, including infections with mycobacteria, bacteria or fungi, and systemic diseases such as granulomatosus with polyangiitis, sarcoidosis, and polyarteritis nodosa.

The optimal treatment for IGM remains unclear, but a lack of benefit from non-targeted antibiotic treatment has generally been accepted (1,9). Until recently, most patients were treated with wide surgical excision or total mastectomy, with post-surgical recurrence rates as high as 50% (3,7). High-dose glucocorticoids are often used, but are not without complications, including difficult wound healing and recurrence when stopped (7,10). Methotrexate has been used as a second line treatment in patients with refractory disease, but has rarely been used as monotherapy. Available reports on the use of methotrexate have used low doses and not evaluated monotherapy. Nonetheless, complete remission rates with methotrexate treatment range between 70-80% and relapse rates are significantly lower compared to reports of surgical resections and prednisone use (2,7,9).

Based on our initial experience using methotrexate as monotherapy for the treatment of IGM (11), patients have continued to be treated in this fashion at our institution. With further time and additional patient referrals we now report on a larger cohort of patients treated with methotrexate as monotherapy for IGM.

Patients and Methods

Institutional Review Board approval was obtained from Stanford University, protocol number 39416. The Stanford Translational Research Integrated Database Environment was queried to identify patients for inclusion in this study if they were evaluated by the Rheumatology Clinic, had histopathologically-established IGM, were treated with methotrexate, and had at least one follow up appointment at the clinic. Additionally, patient demographics,

medical history, IGM history, imaging, and duration and outcome of methotrexate treatment was collected. Improvement (positive change in symptoms from the prior visit) and/or remission (complete resolution while on therapy) of disease was defined by patient and provider assessment of clinical manifestations as documented in the medical record. Relapse was defined as worsening of disease on treatment or recurrence of disease after completion of treatment. Medication compliance was assessed by patient report and all patients were required to be on a contraceptive method (not including barrier methods) to receive methotrexate treatment.

Results

Nineteen patients were identified who met the inclusion criteria (Table 1). All patients were female with an mean age of 33.5 years at the time of presentation. The majority were Hispanic (57.9%), followed by Asian (21.1%), African American (10.5%), and Caucasian (10.5%). The mean parity at presentation was 2 children with a latency between the last pregnancy and diagnosis of 30 months. Two patients (10.5%) were nulliparous. Ten patients (52.6%) reported prior use of hormonal contraception. Two patients (10.5%) had preexisting rheumatologic conditions including tenosynovitis and erythema nodosum. No patients reported a history of smoking tobacco. Seventeen patients (89.5%) had a negative Quantiferon Gold blood test; two patients had a history of treated tuberculosis. Mean time from presentation to diagnosis was six months. Presenting symptoms were unilateral in 13 patients (68.4%) and included breast pain/tenderness (68.4%), mass/lump (47.3%), swelling (21.1%), erythema (21.1%) and induration (15.8%). Most patients had prior unsuccessful treatments with antibiotics (89.5%), incision and drainage (42.1%), prednisone (36.8%), methotrexate (10.5%) and surgical intervention (5.3%) (Table 2).

Methotrexate dosing was started at 10-15mg/week and increased to 20-25mg/week given per oral (PO) or subcutaneous (SC) routes based on clinical response. The mean methotrexate dose in the first 12 months of treatment was 18mg PO weekly. Subcutaneous methotrexate was used if the patient failed oral methotrexate prior to presentation to our clinic, had disease relapse under our management, or reported GI side effects; otherwise, an oral preparation was used.

Within the first three months of treatment, 18 patients (94.7%) noted improvement of their disease with escalating doses of methotrexate as monotherapy. At six months, 94.4% had disease improvement and 22.2% were in remission. By 15 months of treatment, 94% had improved disease and 75% achieved disease remission. Median duration of treatment was 13-15 months (range 1-30 months). At the time of manuscript submission, 12 of 19 patients demonstrated no evidence of disease and remained disease free at follow up on average (and median) of 3 years (range 1-7 years), 4 had ongoing treatment, 2 were lost to follow up (one moved away), 1 failed to improve on treatment (Table 2). Three patients experienced side effects: 2 (10.5%) with nausea and one (5.2%) with elevated liver function tests. The former resolved with switching to subcutaneous administration, and the latter with a decreased treatment dose. The most common reason for termination of methotrexate treatment was disease remission.

A total of three patients (15.8%) had disease relapse while on methotrexate treatment. One patient relapsed between 7-9 months when methotrexate was held due to lapse in contraception and elevated liver function tests. Continuation of methotrexate at a lower dose and subsequent increase, resulted in disease remission. The other two patients relapsed between 10-12 months of treatment, but improved with changing to subcutaneous methotrexate. One

additional patient had disease recurrence off therapy during pregnancy. Only one patient (5.3%) failed to improve on methotrexate therapy and underwent mastectomy.

Discussion

Six decades after its initial characterization, IGM continues to be a devastating, disfiguring disease, lacking standardized treatment. Surgical interventions continue to be practiced despite high recurrence rates. In both our practice and the literature, incision and draiange without adjuvant treatment is never curative; after wide surgical excision, recurrence occurs in up to half of patients (3,7). The one patient in this study who underwent mastectomy experienced return of IGM within one year. While glucocorticoids are commonly initiated as the primary medical therapy for IGM, they have been used with limited success, unwanted side effects and high rates of recurrence (7,10). In our previously reported cases of IGM treated successfully with methotrexate monotherapy, moderate doses of oral weekly methotrexate resulted in shrinking of the breast mass and accompanying symptoms over a period of months (11).

Of the 19 treated patients, 94% demonstrated notable improvement and 75% had disease resolution with the use of methotrexate as monotherapy. Only 15.8% of patients relapsed on treatment, but continued to improve/resolve when changed to subcutaneous administration. One patient relapsed during pregnancy, suggesting hormonal influences on disease. This cohort has comparable racial, age, and diagnostic findings to other published IGM cohorts (1,2,7,10).

In our 10 years of treating IGM with methotrexate, rapid and sustained responses occur with methotrexate doses between 15-25mg PO or SC weekly for 12 months followed by gradual tapering over an additional 6-12 months, for a total of 18-24 months of treatment. Prior steroid

treatment did not impact methotrexate efficacy. The average time from presentation to diagnosis did not change the treatment outcome making a treatment effect with timing unlikely. Furthermore, the use of methotrexate was associated with mild and easily reversible side effects. The limitations of our study include a small sample size and its retrospective nature.

High recurrence rates after surgical interventions and increasing evidence for a local autoimmune disease pathogenesis have resulted in an increased volume of IGM referrals from gynecologists and breast surgeons to rheumatology colleagues (3,12). While a few cases report treatment success with azathioprine or mycophenolate (7,13), prior studies (2,7,9,11) and our current cohort demonstrate high level of efficacy of methotrexate. A commercially available, well tolerated, and easily monitored therapy, methotrexate is commonly used in rheumatology practice. Evidence of methotrexate utility in the treatment of IGM emphasizes the novel and integral role of the rheumatologist as a member of the multidisciplinary team required to care for IGM patients.

References

1. Barreto DS, Sedgwick EL, Nagi CS, Benveniste AP. Granulomatous mastitis: etiology, imaging, pathology, treatment, and clinical findings. Breast Cancer Res Treat 2018;171:527-534.

2. Akbult S, Yilmaz D, Bakir S. Methotrexate in the management of idiopathic granulomatous mastitis: review of 108 published cases and report of four cases. Breast J 2011;17:661-668

3. Uysal E, Soran A, Sezgin E. Factors related to recurrence of idiopathic granulomatous mastitis: what do we learn from a multicenter study? ANZ J Surg 2018;88:635-639.

4. Helal TEA, Shash LS, Saad El-Din SA, Saber SM. Idiopathic granulomatous granulomatous mastitis: cytologic and histologic study of 65 Egyptian patients. Acta Cytologica 2016;60:438-444.

5. Sheybani F, Naderi HR, Gharib M, Sarvghad MR, Mirfeizi Z. Idiopathic granulomatous mastitis: long-discussed but yet-to-be-known. J Autoimmun 2016;49:236-239.

6. Fazzio RT, Shah SS, Sandhu NP, Glazebrook KN. Idiopathic granulomatous mastitis: imaging update and review. Insights Imaging 2016;7:531-539.

7. Sheybani F, Sarvghad MR, Naderi HR. Treatment for and clinical characteristics of granulomatous mastitis. Obstet Gynecol 2015;125;801-807.

8. Troxell ML, Gordon NT, Doggett JS, Ballard M, Vetto JT, Pommier RF, et al. Cystic neutrophilic granulomatous mastitis association with gram-positive bacilli and corynebactrium. Am J Clin Pathol 2016;145:635-645.

9. Azlina AF, Ariza Z, Arni T, Hisham AN. Chronic granulomatous mastitis: diagnostic and therapeutic considerations. World J Surg 2003;27:515-518.

10. Aghajanzadeh M, Hassanzadeh R, Sefat SA, Alavi A, Hemmati H, Delshad MSE, et al. Granulomatous mastitis: presentations, diagnosis, treatment and outcome in 206 patient from the north of Iran. Breast J 2015;24:456-460.

11. Schmajuk G, Genovese MC. First report of idiopathic granulomatous mastitis treated with methotrexate monotherapy. J Rheumatol 2009;36:1559.

12. Skandarajah A, Marley L. Idiopathic granulomatous mastitis: a medical or surgical disease of the breast? ANZ J Surg 2015;85:979-982.

13. Di Xia F, Ly A, Smith GP. Mycophenolate as a successful therapy for idiopathic granulomatous mastitis. Dermatol Online J 2017;23.

Figure Legend:

Figure 1. 34 year old woman with granulomatous mastitis. A. After four months of treatment with antibiotics and prednisone, prior to treatment with methotrexate. B. After 18 months of treatment with methotrexate.

Table Legend:

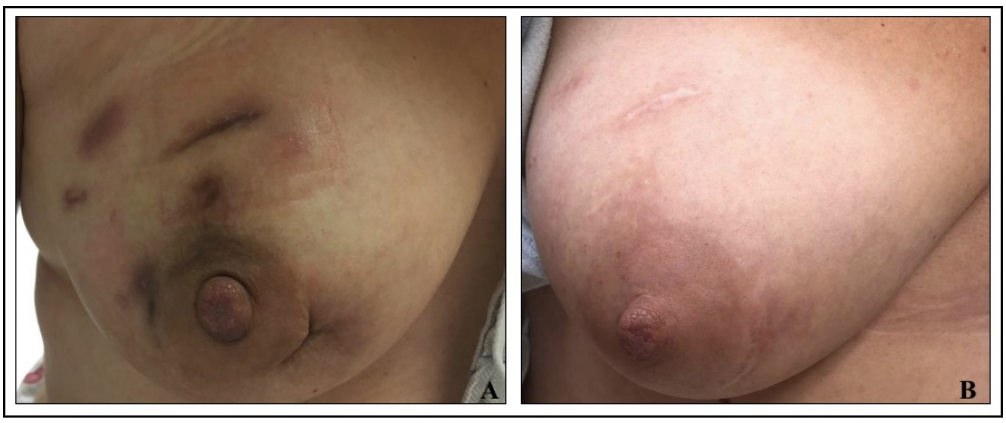
Table 2. Disease history and treatment outcomes in 19 patients treated with methotrexate. Reason for treatment cessation is noted unless therapy was considered complete and stopped by treating physician.

P: pain, E: erythema, S: swelling, M: mass, I: induration; Abx: antibiotics, Pred: prednisone, I&D: incision and drainage, Exci; excision, MTX: methotrexate, mo: months, NED: no evidence of disease; GM: granulomatous mastitis.

Table 1. Main Characteristics of 19 Patients with Granulomatous Mastitis	
	No. (%)
Female Sex	19 (100)
Mean Age at Presentation (years)	33.5
Race	
Hispanic	11 (57.9)
Caucasian	2 (10.5)
African American	2 (10.5)
Asian	4 (21.1)
Mean Age at Menarche (years)	11.8
Preexisting rheumatic disease	2 (10.5)
Prior use of hormonal contraception	10 (52.6)
Negative Quantiferon Gold Test	17 (89.5)
Mean parity at diagnosis	2
Mean Time between last pregnancy and presentation (months)	30
Unilateral disease	13 (68.4)

Table 2. Disease History and Treatment Outcomes

Patient	Time to diagnosis (mo)	Presenting Symptoms	Prior Treatments (mo)	Average MTX Dose (mg)	Treatment Duration (mo)	MTX Treatment Outcome
1	2	P, E, S, M	Abx	15	25-30	Remission at 7-9 mo; NED on 5 year follow up
2	5	P, S	None	9	22-24	Remission at 10-12 mo; NED on 2 year follow up
3	4	P	Abx I&D	15	25-30	Remission at 7-9 mo; NED on 5 year follow up
4	53	P, E, S,	Abx, Pred, I&D	13	4-6	Improvement; treatment ongoing
5	5	P, S, I	Abx, Pred, I&D	21	19-21	Initial improvement on PO, relapsed at 10-12 mo; changed to SC with improvement at 13-15 mo; NED on 19-21 mo follow up, treatment ongoing
6	1	I	Abx, Pred	14	13-15	Remission at 7-9 mo; pt stopped therapy when wanted to conceive. NED on 2 year follow up
7	2	M	Pred, MTX	11	10-12	Remission at 4-6 mo; pt stopped treatment; NED 7 years
8	1	E, P	Abx, Pred	11	16-18	Remission at 13-15 mo; pt stopped treatment; NED on 3 year follow up
9	12	P, M	Abx, Pred, MTX, Exci, I&D	18	19-21	Previously on PO without improvement. Started on SC with remission at 7-9 mo and subsequent relapse when medication held for no birth control and elevated LFTs. Restarted SC with remission again at 13-15 mo; NED on 3 year follow up
10	3	M	Abx	23	10-12	Remission at 10-12 mo; pt stopped treatment; NED 1 year follow up
11	3	P	Abx, I&D	20	10-12	No improvement on PO or SC therapy, underwent mastectomy
12	2	P, E, M	Abx	15	7-9	Remission at 4-6 mo; patient stopped treatment; NED 3 year follow up
13	1	M	None	15	22-24	Improvement; treatment ongoing
14	9	M	Abx	20	4-6	Improvement; lost to follow up
15	3	M	Abx	13	4-6	Remission at 4-6 mo, patient stopped treatment; NED on 3 year follow up
16	1	P, M	Abx, I&D	20	1-3	Improvement at 1-3 months; moved out of state
17	1	P, M	Abx	21	19-21	Remission at 4-6 mo; patient stopped treatment; NED 19 month follow up
18	3	P	Abx, Pred, I&D	18	7-9	Improvement 7-9 mo, NED at 10-12 months. Changed healthcare system – new lesion on left breast without treatment not thought to be GM
19	2	P, E, I	Abx, I&D	21	16-18	Initial improvement then relapse at 10-12 mo, started on SC with improvement, changed to PO at 16-18 months and remission by 24 mo. 1 year later flare during pregnancy



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