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DEVELOPMENT AND INITIATION OF A CLINICAL PROTOCOL FOR THE TREATMENT OF IDIOPATHIC GRANULOMATOUS MASTITIS

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ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is an uncommon benign chronic inflammatory breast lesion, characterized histologically by noncaseating granulomatous inflammation. It presents a challenging clinical scenario, as it can mimic breast carcinoma on imaging and physical examination. The etiology, clinical course, and optimal treatment of this disorder remain unclear.

Objective: The goal of this study was to develop a clinical protocol based on optimal response to therapies utilized for the treatment of IGM.

Methods: Hospital records were reviewed for granulomatous mastitis demonstrated on pathology. Charts were reviewed for demographic information, history with regard to potential triggers, clinical data on presentation, courses of treatment, and response to therapy. Time to clinical resolution was analyzed with the Kaplan-Meier method. Clinical protocol was subsequently developed after careful analysis of response, with a focus on minimizing morbidity.

Results: IGM was identified in 23 women: mean age was 33.6 years, 82.6% were premenopausal, 95.6% were Hispanic, and 78.3% were multiparous. Of these patients, 95.2% presented with a palpable mass, along with associated skin changes (59.1%), pain (59.1%), and nipple discharge (22.7%). On examination or imaging, 69.6% of patients had a mass >3 cm, with a median Breast Imaging Reporting and Data System score of 4 on initial imaging. Ten patients received a single form of therapy, while 11 patients received multimodal therapy. Two patients were followed up expectantly. Treatment modalities included antibiotics, oral steroids, aspiration, surgery, and topical steroids, with antibiotics and oral steroids the most common primary therapies. Oral steroid treatment was more likely to result in clinical response (80.0%) than were antibiotics (44.4%). Median time to clinical resolution was 21.4 months.

Conclusions: IGM remains a difficult clinical entity with unknown etiology. While this disorder appears to be self-limited, clinical course is often prolonged. Core needle biopsy is reliable for establishing the diagnosis and excluding malignancy. Expectant management is ideal, with therapy aimed at improving symptoms while limiting morbidity of treatment.

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is an uncommon chronic inflammatory breast lesion first described in 1972 by Kessler and Wolloch.[1] While it is a benign diagnosis, it presents a clinical problem, as it can simulate breast carcinoma on imaging and physical examination.[2] Despite published literature spanning almost 40 years with more than 500 cases documented, the etiology, clinical course, and optimal treatment of this disorder remain unclear.[3]

Definitive diagnosis of IGM is made only after histologic confirmation of noncaseating granulomatous inflammation in the breast lobules with or without associated microabscesses (**Figure 1**).[3,4] Pathologic features may overlap with other infectious or noninfectious causes of granulomatous disease in the breast, such as infection with Mycobacterium tuberculosis, sarcoidosis, Wegener's granulomatosis, fungal infections, and others.[5]

IGM typically affects young parous women of childbearing age, although it has been described in patients as young as 11 and as old as 80 years of age.[6] Associations have been made in previous studies between IGM and pregnancy, lactation, and oral contraceptive (OC) use, but no definite causality has been defined. IGM is thought to have an autoimmune etiology, with inflammatory response to an inciting

agent, possibly extravasated milk protein, a local chemical irritant, local trauma, environmental exposure, or a viral infection.[7]

The treatment of IGM includes systemic steroids,[3,8] antibiotics,[8] surgical excision,[9,10] and other immunosuppressive agents such as methotrexate.[3,4] The disease process tends to be chronic, and can lead to significant cosmetic deformity as well as diminished quality of life for women with this diagnosis.[3] There is currently no consensus on optimal therapeutic interventions and the order in which they should be initiated. Anecdotal clinical experience revealed an unusually large number of patients with a diagnosis of IGM presenting for management at our institution. Because of the lack of published guidance on treatment of this disease, we performed a review of our experience with IGM to optimize clinical protocols.

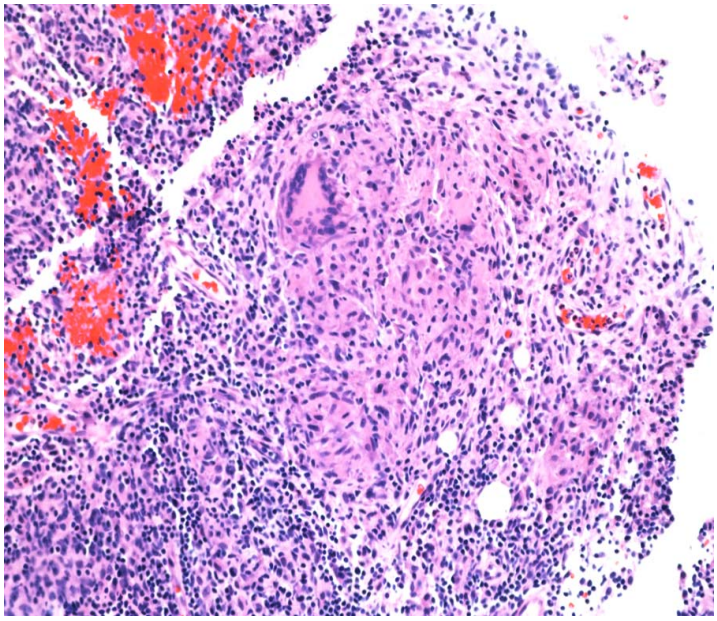

Figure 1. Granulomatous inflammation with giant cells, magnification X 20, H&E

METHODS

An institutional review board–approved, retrospective search of electronic medical records spanning 2006 to 2013 for Parkland Memorial Hospital, Dallas, Texas, was conducted. Parkland Hospital is a county hospital that serves a primarily uninsured, minority population. Records were searched for the diagnosis of "granulomatous mastitis." Twenty-three patients were identified who had core needle biopsy demonstrating the characteristic pathologic findings of noncaseating, granulomatous inflammation of the breast lobules. Exclusion of tuberculous or fungal causes of granulomatous mastitis was performed using histologic staining for acid-fast bacilli and Grocott's methenamine silver staining.

Medical records were reviewed for demographic information (age at diagnosis, race/ethnicity, sex), history (pregnancy, menopausal status, history of breastfeeding, time from last live birth to presentation of IGM, OC use, smoking history), clinical data (presenting symptoms, size/location of mass, presence of skin changes, clinical impression on presentation, initial Breast Imaging Reporting and Data System [BIRADS] status, review of pathology, cultures) and treatment data (courses of therapy, use of steroids/antibiotics/surgery, number of clinic visits/emergency department visits, time to resolution of process, status of disease at last follow-up). Response to individual courses of therapy was obtained from clinical documentation, with positive clinical response defined as any subjective improvement in the patient's symptomatology, or objective improvement in examination findings at the time of follow-up. A time to clinical resolution of disease curve was generated with Kaplan-Meier methods for time to event using Prism 6 software (GraphPad Software, San Diego, CA).

RESULTS

Demographics

Idiopathic granulomatous mastitis affected primarily young women (age range, 21–53 years; mean age, 33.6 years) (**Table 1**). Three women were perimenopausal and 1 woman was postmenopausal at presentation. All patients except 1 were Hispanic (95.6%). Information regarding previous pregnancies was available for 20 of 23 patients; 18 of 20 were multiparous, with 2 patients having IGM diagnosed following their first pregnancy, and 1 woman was nulliparous. Information on time from last live birth to diagnosis of IGM was available for 15 of 23 patients. A majority of patients (56.5%) had given birth in the 5 years preceding diagnosis of IGM, with the most common interval 2 to 5 years following the last live birth. Information on OC use was available for 15 patients; 11 of 15 had taken OCs at some point prior to diagnosis of IGM. Only 1 patient was identified as a smoker.

Table 1. Clinical Characteristics of Patients

Age		
Range	21-53 years	
Mean	33.6 years	
Race/ethnicity	**Number of Patients**	**Percent of Patients**
Hispanic	22	95.6
Black	1	4.3
Menopausal Status		
Premenpausal	19	82.6
Perimenopausal	3	13.0
Postmenopausal	1	4.3
Parity		
Nulliparous	1	4.3
Primiparous	2	8.7
Multiparous	18	78.3
Time from last live birth to presentation of IGM		
<1 year	1	4.3
1 to 2 years	4	17.4
2 to 5 years	8	34.8
>5 years	2	8.7
Unknown	8	34.8
Prior OC use		
Yes	11	47.8
No	4	17.4
Unknown	8	34.8
History of breastfeeding		
Yes	10	43.5
No	1	4.3
Unknown	12	52.2
Smoking history		
Previous smoker	1	4.3
Never used	22	95.7

IGM, idiopathic granulomatous mastitis, OC, oral contraceptive.

Presentation

All of the patients except 1 presented with a palpable finding, while 1 patient presented with recurrent, persistent breast pain only, with no palpable abnormality (**Table 2**). Twenty of 23 patients (87.0%) presented with associated symptoms in addition to the mass: pain and skin changes (56.5% each), erythema (39.1%), nipple discharge (21.7%), and axillary lymphadenopathy (13.0%) at presentation. All patients underwent breast imaging, with a median BIRADS score of 4. The largest size of the IGM process was >5 cm in 8 patients (34.8%), 3 to 5 cm in 8 patients (34.8%), 2 to 3 cm in 4 patients (17.4%), and <2 cm in 3 patients (13.0%). Five patients had persistent drainage from the core needle biopsy site, while 1 patient developed a spontaneously draining sinus tract prior to biopsy.

Treatment

The median number of courses of therapy was 2 (range, 0 –8). Ten patients received a single form of therapy, while

Table 2. Clinical Characteristics of IGM on Presentation.

Characteristic	**Number of Patients**	**Percent of Patients**
Signs/symptoms at presentation		
Pain	13	56.5
Skin Changes	13	56.6
Erythema	9	39.1
Nipple discharge	5	21.7
Lymphadenophathy	3	13.0
Largest size of IGM process		
<2 cm	3	13.0
2 to 3 cm	4	17.4
3 to 5 cm	8	34.8
>5 cm	8	34.8

IGM, idiopathic granulomatous mastitis.

11 patients received multimodal therapy. Initial therapy was with antibiotics in 9 patients, oral steroids in 7 patients, aspiration in 4 patients, and surgery in 1 patient. Two patients were followed up expectantly without intervention.

Thirteen of 23 patients received antibiotics during their course of treatment, 6 receiving more than 1 course, for a total of 18 courses of antibiotics used (**Figure 2**). Clinical response was noted in 44%. Cultures were obtained from 6 of 23 patients through aspiration or operative drainage. One culture returned corynebacteria, while the remainder showed no growth of microorganisms, with an inflammatory infiltrate of white blood cells on Gram stain.

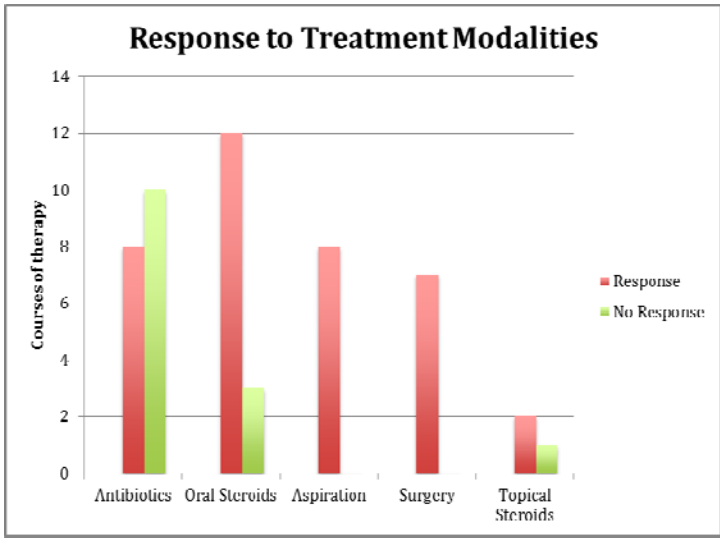

Figure 2. Clinical response to treatment modalities.

Ten patients received oral steroids; 5 received multiple courses of oral steroids. Clinical response was noted in 80%. No cases of steroid-induced diabetes were noted. There was no use of methotrexate or any other immunosuppressive agent. Three courses of topical steroids were used in 2 patients, with clinical response in 1 patient.

Six patients had aspiration of the breast, and 2 received multiple aspirations. Clinical response was noted for each of the 8 instances. Five patients underwent a total of 7 surgeries. One patient underwent partial mastectomy, while the remainder of cases had simple incision and drainage procedures. The partial mastectomy was performed for a patient with a limited area of IGM (<3 cm with no overlying skin changes); clinic notes reflect that this was the patient's preference. She had clinical resolution of IGM, with no wound morbidity, and no evidence of disease at last follow-up. Two patients experienced wound morbidity, with persistent drainage from the incision and drainage site. Three of 5 patients who underwent surgery had eventual clinical resolution, with no evidence of disease at last follow-up.

Two patients did not receive any therapy, noting that their symptoms had improved from the time of presentation to their first visit to the breast clinic. These 2 patients had expectant management with follow-up; 1 had no clinical evidence of disease on final follow-up (4.1 months from presentation), while the other was clinically improving on final follow-up (3.5 months from presentation).

Only one recurrence was observed: a patient who was followed up through resolution on the affected side returned with contralateral disease 2 years from initial presentation. The initial treatment modality did not seem to predict resolution (**Table 3**), nor did any combination of treatment modalities (**Table 4**).

At a median overall follow-up of 26.6 months, 11 patients (47.8%) had no clinical evidence of disease compared with 12 (52.2%) with persistent disease. Overall median time to clinical resolution (T50) was 21.4 months (**Figure 3**). Median time to resolution for the group with resolution of disease was 17.0 months. Median length of follow-up for the group with resolution of disease was 34.9 months versus 11.9 months for those with persistent disease.

Table 3. Initial Treatment Modality and Clinical Resolution

Initial Treatment Modality	Resolution	Stable Disease
No therapy	1	1
Antibiotics	4	5
Oral steroids	3	4
Aspiration	2	2
Surgery	1	

Table 4. Combinations of Treatment Modalities and Clinical Resolution

Treatment Modality	Resolution	Stable Disease
No therapy	1	1
Antibiotics	2	1
Oral steroids	2	1
Aspiration	2	1
Surgery	1	
Antibiotics + oral steroids	1	2
Antibiotics + aspiration		1
Antibiotics + surgery	2	
Antibiotics + oral steroids + surgery		2
Antibiotics + oral steroids + aspiration		1
Oral steroids + aspiration		1
Oral steroids + topical steroids		1

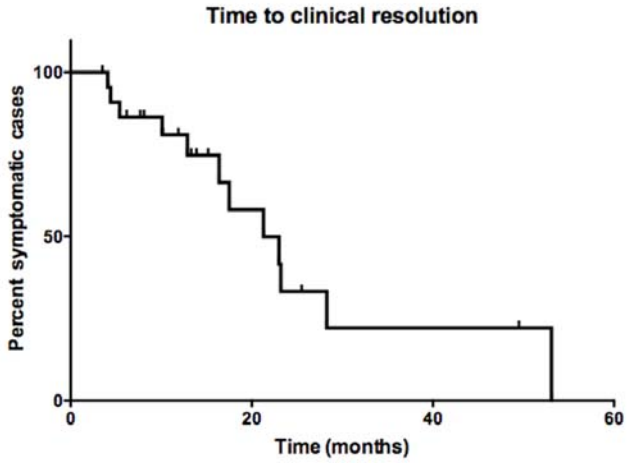

Figure 3. Kaplan Meier curve of time to clinical resolution of disease.

DISCUSSION

This series represents one of the largest reported cases of IGM treated at a single institution in the United States. The patients in this case series were almost uniformly Hispanic, which is disproportionate to our clinic demographics, as Hispanics represent 40% of the population served by the Parkland breast clinic.[11] Previous studies suggest that IGM is more common in nonwhites,[12] and the largest series exist in the developing world. This led us to question the timing of immigration in these patients; however, immigration status could not be readily determined from clinic records. We plotted the residences of the patients by zip code to evaluate for a possible common environmental exposure, but found that they were evenly distributed across the metropolitan area (data not shown).

Similar to other series, most of our patients were young, premenopausal, multiparous, and had given birth in the preceding 5 years.[12] Prior pregnancy, lactation, OC use, and smoking were specifically explored, as they have been previously associated with IGM. The association of IGM with parity/lactational change of the breast is demonstrated in this series. Interestingly, 3 patients who were followed up until clinical resolution of IGM have had subsequent pregnancies, and none of these patients has developed recurrence after their pregnancy. Only 1 patient was a smoker, in contrast with periductal mastitis, which is strongly associated with smoking.[13]

Our data reinforce the chronicity of IGM. Patients had a mean 5.37 clinic visits per patient/year related to IGM. The chronic nature of complaints with IGM and the varying response rates to therapy are a frustration for both patient and physician. Long duration of medical therapy, cosmetic deformity after surgery, and the possibility of recurrence are important quality-of-life issues. Uncertainty regarding the etiology of disease and persistent symptoms have led to a spectrum of treatment recommendations, from observation[20] to mastectomy.[9]

Antibiotics were frequently used in this series, most commonly in the primary care/emergency department setting, with a limited clinical response rate. Superinfection appears to be relatively rare, with Gram stain and culture results in our series most commonly showing an inflammatory infiltrate devoid of organisms with negative culture results. One patient had a positive culture for an undefined species of Corynebacterium. This bacteria has been associated in other studies as a possible infectious cause of granulomatous mastitis,[7] but establishing causality remains difficult as it is common to skin flora, and its fastidious nature makes it difficult to culture.[14] Sensitive polymerase chain reaction–based assays failed to identify Corynebacterium in a cluster of cases of IGM affecting a similar population of US-based Hispanic women.[15]

DeHertogh et al first described use of corticosteroid therapy for treatment of IGM in 1980.[16] Since that time, several series have documented the use of oral steroids, typically prednisone or prednisolone, with varying response rates. In 2009, Sakurai et al reported a series of 8 patients receiving steroids for IGM; 7 of the 8 patients had clinical resolution of IGM without surgery.[17] However, the mean duration of steroid treatment was 7.7 months, with other reports in the literature of duration of steroid therapy of up to 22 months prior to clinical resolution, leading investigators to explore the option of alternative immunosuppresants such as methotrexate to decrease the morbidity from long-term medical treatment with steroids.[4]

Steroid therapy was the second most common intervention in this series, and was typically prednisone 30 mg/day, for 2 weeks duration with a taper. Although steroids appeared to have a better clinical response rate than did antibiotics at interval follow-up, this did not predict clinical resolution, as 7 patients with positive clinical response to steroids still had clinically evident disease at the time of the last follow-up. No steroid-related morbidity, such as steroid-induced diabetes, was

noted in this series. Topical steroids were utilized following positive experience reported in a case report.[18] Methotrexate was not used because of the difficulty in assuring proper contraception and surveillance for hematologic toxicity in our population.

Despite early reports that surgery was often complicated by high recurrence, fistula formation, and wound infection,[12] Asoglu et al describes 18 patients treated with wide local excision or quadrantectomy plus antibiotics; at a median 36-month follow-up, only 1 patient developed a recurrence.[19] Initial surgical therapy is often not possible without cosmetic deformity; in our series, the majority of patients had lesions >3 cm in size, with nearly all patients having associated skin changes. Initial surgery in our group of patients would have resulted in poor aesthetic outcome. A recent multimodality strategy proposed by Gurleyik et al involves initial steroid therapy for 8 weeks to decrease the size of IGM lesions, followed by wide local excision, citing lack of complete response to steroids alone, and relapse or recurrence rates of 16% to 50%.[10] This is attractive conceptually in that it mirrors the treatment of locally advanced malignant disease, with use of neoadjuvant therapy to reduce the extent of surgical resection.

Variability in response to treatment may indicate that patients with IGM are still a heterogeneous group. Core needle biopsy was reliable for the diagnosis of IGM in our series and the exclusion of malignancy. No patient in this study had evidence of neoplasia or hyperplasia/atypia noted on core biopsy, and no patient has developed breast cancer subsequently.

Two studies give us insight into the natural history of IGM. Lai et al followed up 8 patients expectantly without treatment.[20] Four had spontaneous resolution at a median interval of 14.5 months, and 4 had stable disease, with a median follow-up of 11 months. Al-Khaffaf et al reported on a series of 18 patients with IGM over a 25-year period, noting that all had eventual clinical resolution of disease.[12] Our data are comparable in that among those who had resolution of disease, median time to resolution was 17 months. Length of follow-up was shorter among those who still had evidence of disease at final follow-up, a median of 11.9 months, suggesting that more patients would progress to resolution with longer follow-up.

This study was conducted to review internal practice in the care of patients with IGM; however, it is limited by its retrospective nature. Response to treatment was obtained from chart review and could not be further objectively quantified. Most patients in this series were symptomatic at presentation, with symptoms driving the need for treatment. As this disorder seems to be self-limited, treatment should be aimed at improving symptoms while limiting morbidity of therapy.

Our treatment strategy has evolved in light of these findings. We have outlined a treatment algorithm, which we have begun to use in our clinic (**Figure 4**). Once the diagnosis of IGM has been made, antibiotics are appropriate only when systemic signs of infection, fever, or leukocytosis are present. Before use of systemic immunosuppressants, we propose starting therapy with a trial of topical steroids, and aspiration of any associated fluid collection under ultrasound in an attempt to control symptoms. Surgery may be considered for small, localized areas amenable to wide local excision only in an attempt to limit systemic toxicity from long-term steroid therapy.

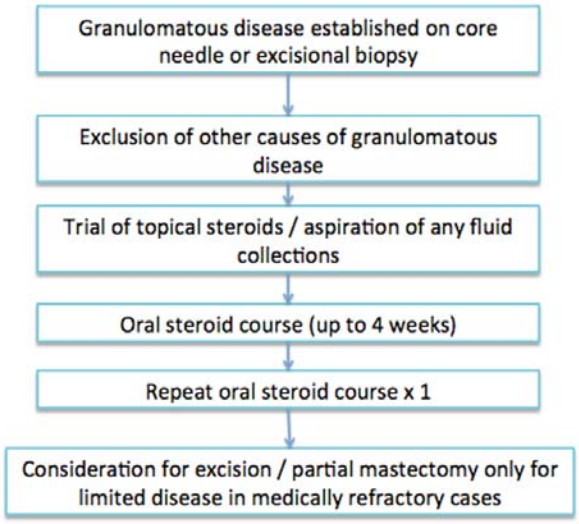

Figure 4. Proposed initial treatment algorithm

CONCLUSIONS

IGM remains a difficult clinical entity to treat. The clinical course of patients with IGM is often prolonged. Exclusion of malignancy as well as specific causes of granulomatous mastitis is essential before pursuing conservative therapy for IGM. Core needle biopsy is reliable for establishing the diagnosis and excluding malignancy. The disorder is often self-limited, and treatment should be aimed at alleviating symptoms, with attention to limiting morbidity of treatment.

ACKNOWLEDGMENTS

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