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ORIGINAL SCIENTIFIC REPORT

Granulomatous Mastitis and Factors Associated with Recurrence: An 11-Year Single-Centre Study of 113 Patients in Singapore

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Abstract

Background Granulomatous mastitis (GM) is an inflammatory breast disease of unknown aetiology. It poses diagnostic and therapeutic challenges with myriad forms of clinical presentation, varying results to treatments and propensity to recur. This study aims to look at clinical and treatment factors that predispose to recurrence of GM.

Methods We performed a retrospective review of 113 patients in our unit with histologically proven GM from 2006 to 2016. Demographic, clinical, treatment and outcomes data were collected and analysed.

Results Eighty-nine patients were treated with antibiotics (78.8%), 79 (69.9%) with steroids and 23 (20.4%) patients underwent surgery. Twenty (17.7%) patients had recurrence. Patients who presented with inflammatory signs and symptoms had increased odds of having subsequent recurrence: skin changes (1.50), pain (2.00), fistula (4.39) and antibiotic treatment (6.65). Four patients (20%) with recurrence had positive bacterial cultures. All 4 grew *Corynebacterium*. Patients with *Corynebacterium* infection had a 2.64 times higher risk of recurrence. Surgery did not preclude recurrence. There was a 70% (7/10) penicillin resistance rate in our patients with positive cultures for *Corynebacterium*.

Conclusion Initial presentation with inflammatory signs and symptoms may confer increased risk of recurrence, warranting closer monitoring. *Corynebacterium* infection may play a part as a causative factor and risk factor for recurrence. Non-penicillin antibiotics should be considered as first-line antibiotics for patients presenting with inflammatory changes. Further prospective studies with larger patient populations might reveal information on the aetiology of GM and result in the development of a more standardized and effective treatment regimen.

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Introduction

Granulomatous mastitis (GM) is a rare, benign, chronic inflammatory breast disease of unknown aetiology. First described by Kessler and Wolloch in 1972 [1], it continues to perplex clinicians with myriad forms of clinical presentation, varying results to a wide range of treatments and propensity to recur.

Although GM is frequently thought to be idiopathic in nature, several aetiologic factors have been hypothesized but an exact cause remains elusive.

An autoimmune mechanism is widely favoured [2] and supported by documented response to steroid treatment [3–7]. However, studies so far have not demonstrated any correlation between known autoimmune markers and diagnosis or severity of GM [3, 8, 9]. Through immunohistochemical studies, the role of an autoimmune mechanism is bolstered by predominance of T-lymphocytes that demonstrate an autoimmune pathological process involving T-cell-mediated inflammation and granuloma formation [3, 10, 11].

Although most cases of GM are sterile, detection of *Corynebacterium* in GM is increasingly reported [12, 13]. *Corynebacteria* infection is associated with cystic neutrophilic GM [13–15], characterized by lipogranulomas consisting of clear spaces rimmed by neutrophils and surrounding granulomatous inflammation (Fig. 1). Although *Corynebacteria* are a recognized cause of mastitis in livestock, it is generally considered to be non-pathogenic commensals in humans [12, 16] and it can be difficult to distinguish true infection from colonization and contamination. There are, however, features that support infection: strong leucocytic reaction, pure growth on culture and the presence of organisms deep in the breast tissue and within vacuoles surrounded by granulomatous inflammation. The increasingly common and consistent finding of the unusual species *Corynebacterium kroppenstedtii* also supports its role as a probable causative agent [12, 14, 15].

GM most commonly affects women of reproductive age [2, 17, 18] with a history of parity and lactation [19–21]. A proposed mechanism of action is that milk protein within hypertrophic and fragile breast tissue, along with microtrauma from breastfeeding, incites an autoimmune process with formation of non-caseating granulomas [18]. However, most patients were not actively lactating at time of presentation [22, 23]. Cases of GM have also been documented in men and post-menopausal women [24–26]. Hyperprolactinaemia in GM has been reported with a similar mechanism of action [11, 27–30]. However, such cases are too rare with varying results being reported to establish routine serum prolactin measurements as a diagnostic and monitoring tool.

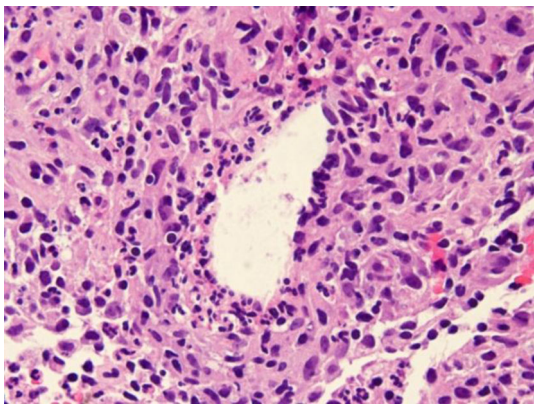

Fig. 1 Cystic space lined by neutrophils and surrounded by epithelioid histiocytes

Patients with GM can present with a wide variety of symptoms such as breast lumps, pain, inflammatory changes of the skin, abscess, fistula (Fig. 2), nipple retraction and axillary lymphadenopathy [18, 31]. There is no pathognomonic characteristic of GM on breast imaging. Mammographic findings include focal asymmetric density, architectural distortion, irregular masses and skin thickening [32–34]. Ultrasonography is frequently the imaging modality of choice and may reveal focal hypoechoic masses, parenchymal heterogeneity, abscess and skin thickening [32–34]. The appearance of GM on magnetic resonance imaging (MRI) has been described though it is rare and not routinely employed in the evaluation of these patients. Specificity is, likewise, poor and no MRI feature is capable of distinguishing between GM and malignancy [34, 35]. Due to this absence of distinct clinical and radiological characteristics, GM lesions have been misdiagnosed as carcinomas, sometimes resulting in mastectomies being performed [10, 36].

Definitive diagnosis of GM is usually achieved through histological evaluation. Common features include the presence of lobulocentric granulomatous inflammation (Fig. 3), giant cells, epithelioid histiocytes, non-caseating granulomas (Fig. 4) and neutrophils [18, 31, 37, 38]. Due to the poor sensitivity of fine-needle aspiration cytology (FNAC), with diagnostic rates as low as 21% being reported [39], histological examination of tissue is the best way of achieving diagnosis of GM.

Several forms of treatment for GM have been described in the literature with no consensus on the optimal management of this disease. Treatments reported include observation [40, 41], pharmacological treatment in the form of antibiotics, immunosuppressants like topical steroids [3], oral steroids [4–7] methotrexate [42–44], dopamine agonists like bromocriptine [28, 45] and cabergoline [27]; surgical treatment including drainage [46], wide local excision [19] or even mastectomy [47]. Due to wide

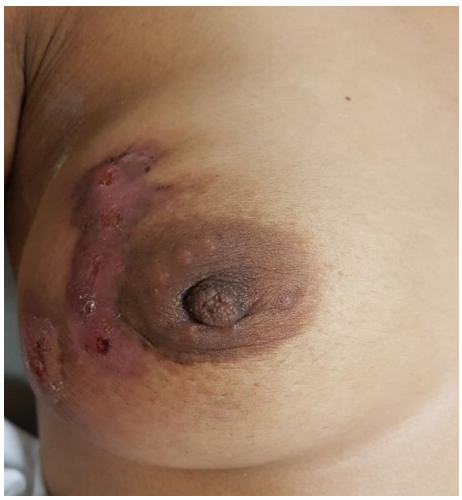

Fig. 2 GM with fistula formation

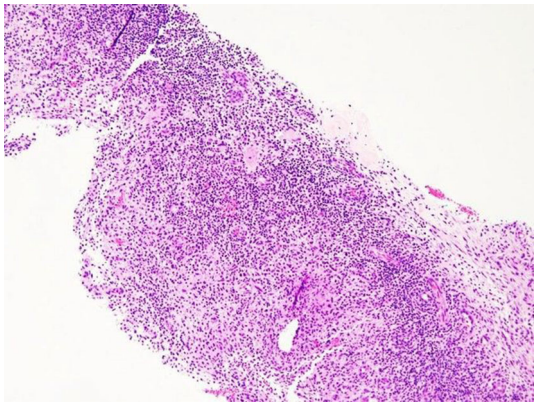

Fig. 3 Lobulocentric granulomatous inflammation

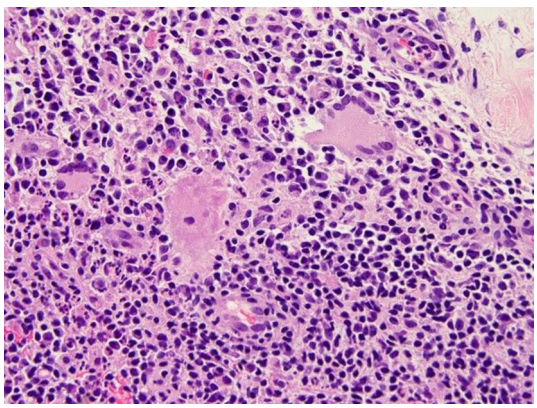

Fig. 4 Granulomas with giant cells epithelioid histiocytes

acceptance of an autoimmune aetiology, corticosteroid therapy is the main form of medical treatment for GM. There have been several suggested regimens but an optimal one has yet to be agreed upon [5, 39, 48, 49]. GM can have a protracted treatment course and is also prone to recurrence [2, 18] with rates ranging from 5 to 50% reported in the literature [3, 8, 20, 31, 33]. Failure to respond to steroids frequently leads to surgical excision although this does not prevent recurrence as well [50, 51].

In view of the increasing recognition of GM and its diagnostic and therapeutic challenges, this study was conducted aiming to look at clinical and treatment factors that could affect the outcomes and recurrence in our patients with GM.

Materials and methods

Data from hospital records, breast imaging, laboratory investigations and treatment history of 113 patients with histologically proven GM from January 2006 to December 2016 were retrospectively collected and analysed. Patients with tuberculous mastitis were excluded. Five patients had bilateral GM resulting in 118 cases of GM. Data collected included clinical presentation, radiological findings, microbial culture results from pus or tissue, histopathological findings, type of treatment administered, duration of treatment, time to resolution, recurrence and duration of follow-up. Imaging included mammography and breast ultrasound. None underwent MRI of the breasts. Disease resolution was defined as either clinical resolution of presenting symptom and/or radiological resolution of the lesion. Time to resolution was defined as the duration from commencement of treatment to the date of resolution. Duration of follow-up was defined as the duration between the date of diagnosis of GM and the date of last review. Recurrence was defined as GM occurring after documented resolution of the initial presenting episode. IBM SPSS version 19 software package was used for statistical analysis. Continuous variables were summarized as mean (sd) or median (IQR) and categorical variables by frequency (%). In order to assess associations between the primary outcome and independent categorical variables, the Chi-squared test or the Fisher's exact test was used. A p value of <0.05 was considered statistically significant. Univariate logistic regression was performed to assess the predictive relationship between individual independent variables and the outcome.

This study was approved by the Centralised Institutional Review Board of SingHealth.

Results

Table 1 summarizes the clinical characteristics, radiological features, histological diagnostic methods, microbial culture results and treatment of the patients.

The mean age of onset was 36.2 years (range 25–63 years). Majority were in the 30–39 age group (62.8%). Ninety-six (85%) patients were parous. Ten (8.8%) had a history of lactation within 6 months prior to diagnosis.

The commonest presenting symptom was a breast lump in 103 patients (91.2%), followed by breast pain in 76 patients (67.3%). Sixty-nine patients presented with a painful breast lump (61.1%). Other presenting symptoms include inflammatory skin changes (erythema, warmth and thickening), fistula formation and fever. Median duration of symptoms was 21 days (1–270).

Fifty-four patients (47.8%) had both mammography and breast ultrasound performed on presentation. Fifty-six (49.6%) had breast ultrasound, and one (0.9%) had mammogram performed only. Radiologically, there was a lack of defining characteristics. GM can take on any appearance ranging from benign looking lesions reminiscent of abscesses (Fig. 5) to having suspicious features resembling a carcinoma (Fig. 6). Eighty-four patients (71.2%) had unifocal disease, 34 (28.8%) had multifocal disease, and 5 (4.4%) had bilateral GM.

All patients had histological diagnosis of GM. Core-needle biopsy (CNB) was the most common method of diagnosis with 95.2% of CNBs successfully diagnosing GM. Only 14.3% of FNACs revealed GM with the rest being diagnosed after CNB or excisional tissue biopsy.

Bacterial cultures were performed in 68 (57.6%) patients. Fifteen patients had positive bacterial culture results (22.1%) of which 12 (80%) grew *Corynebacteria*. Treatment administered varied widely and, 85 patients (75.2%) received multiple forms of treatment.

Most patients, 110 (97.3%), received non-surgical treatment. Eighty-nine (78.8%) patients received antibiotics, 79 (69.9%) received steroids. Thirteen patients (11.5%) were treated with antibiotics only, 12 (10.6%) with steroids only and 41 (36.3%) received both. One patient (0.9%) received methotrexate after failure of antibiotics and steroids. Of the 17 patients treated with antibiotics only, eight were lost to follow-up (47.0%) and four of the remaining nine patients who resolved went on to develop recurrence (23.5%). All 12 patients treated with steroids only achieved resolution.

Twenty-three patients (20.4%) underwent surgery in the form of excisional biopsy (6), vacuum-assisted biopsy (VAB) (6) or incision and drainage (11) of abscess. Of the 23 patients, 20 (87.0%) received surgical treatment after

Table 1 Clinical characteristics, diagnostic findings and treatment of patients with granulomatous mastitis

	Patients (n = 113)	Percentage (%)
Patient demographics		
Age		
Mean (years)	36.2 (25–63)	
Median (years)	36	
Age groups		
20–29	15	13.3
30–39	71	62.8
40–49	24	21.2
50–59	2	1.8
>60	1	0.9
Ethnicity		
Chinese	77	68.1
Malay	16	14.2
Indian	8	7.1
Other ethnic groups	12	10.6
Parity		
Nulliparous	16	14.2
Parous	96	85
Unknown	1	9.2
Lactation within past 6 months		
Yes	10	8.8
No	102	90.3
Unknown	1	0.9
Presenting symptoms		
Breast lump	103	91.2
Breast pain	76	67.3
Inflammatory skin changes	25	22.1
Fistula	5	4.4
Fever	4	3.5
Imaging characteristics		
Imaging type		
Ultrasound breasts only	56	49.6
Mammogram only	1	0.9
Ultrasound breasts and mammogram	54	47.8
No imaging done	2	1.8
Focality	n = 118	
Unifocal	84	71.2
Multifocal	34	28.8
Laterality		
Unilateral	108	95.6
Bilateral	5	4.4
Imaging results	n = 118	
Benign	45	38.1
Indeterminate	42	35.6
Suspicious	28	23.7
Not mentioned	3	2.5

Table 1 continued

	Patients (n = 113)	Percentage (%)
Diagnostic methods		
Fine-needle aspiration cytology	4 (28)	14.3
Core-needle biopsy	99 (104)	95.2
Excision biopsy	12 (12)	100
Tissue from abscess cavity	4 (8)	50
Bacterial cultures performed	68	57.6
Positive cultures	15	22.1
Corynebacterium	12	80
Staphylococcus aureus	2	13.3
Multibacterial growth	1	6.7
Treatment		
Non-surgical	110	97.3
Antibiotics	89	78.8
Steroids	79	69.9
Methotrexate	1	0.9
Surgical	23	20.3
Excision biopsy	6	5.3
Vacuum-assisted biopsy	6	5.3
Incision and drainage	11	9.7
Observation	7	6.2
Outcome		
Recurrence	20	17.7
No recurrence	81	71.7
Lost to follow-up	12	10.6

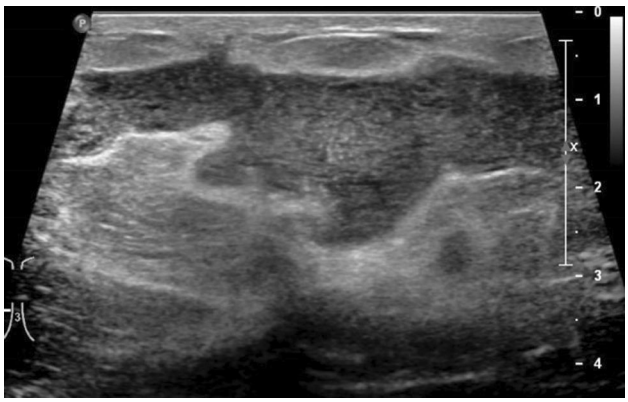

Fig. 5 Irregular hypoechoic mass, likely abscess

failure of medical therapy. Of the six patients who underwent excisional biopsy, four (66.7%) also received non-surgical treatment. Five patients who underwent VAB (83.3%) received non-surgical treatment. All patients who underwent incision and drainage received non-surgical treatment. Seven patients (6.2%) were treated with observation only. Five achieved resolution, and two were lost to follow-up. All seven patients presented with a breast lump, of which 4 of them reported pain. None had inflammatory skin changes.

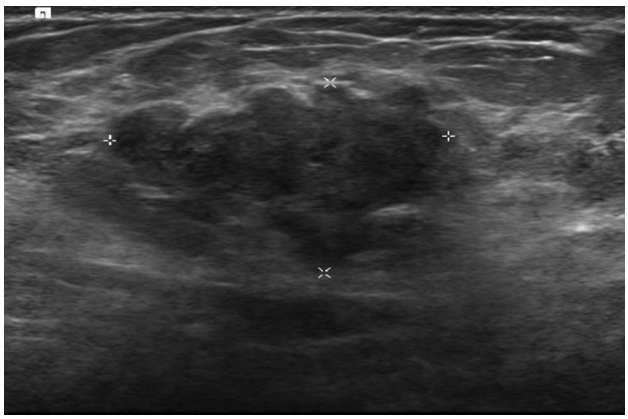

Fig. 6 Heterogenous mass with irregular margins, "hard" on elastography, suspicious for carcinoma

The mean duration of treatment with prednisolone was 17.3 (range 7–448) days and 3.6 (range 7–105) days for antibiotics. 103 patients (91.2%) had improvement with a median time to resolution of 14.5 months. Median follow-up duration was 252 days. Twelve patients (10.6%) were lost to follow-up.

Twenty patients (17.7%) had recurrence of GM (Table 2). Fifteen of them (75%) had initial presentation with a painful lump, of which six had inflammatory skin changes and one had fistulation. Sixteen patients were treated with both antibiotics and steroids and four with antibiotics alone. Four underwent surgery (two excision biopsies and two incision and drainages). Only 4 out of 17 (23.5%) recurrent patients who had bacterial cultures performed had positive results. All positive cultures grew *Corynebacterium*.

Clinical and treatment factors such as duration of symptoms, focality, size of lesion, culture positivity and duration of treatment with antibiotics and steroids did not show statistically significant risk of recurrence on univariate analysis. Presenting with inflammatory signs and symptoms increased the risk of having recurrence (presented in Table 3 as odds ratios): skin changes (1.50), pain (2.00), fistula (4.39). Patients with *Corynebacterium* infection had a 2.64 times increased risk of developing recurrence. Patients who received antibiotics had a 6.65 times increased risk of developing recurrence.

Fifteen (75%) of the patients with recurrent GM achieved resolution. Six of them (40.0%) were treated with antibiotics and oral steroids, one (6.67%) with steroids and one with antibiotics. Seven patients (46.7%) resolved with only observation and all presented with painless breast

Table 2 Clinical and treatment factors between patients with recurrence and no recurrence of granulomatous mastitis

Factors	Recurrence (n = 20)	No recurrence (n = 81)
Symptoms		
Lump	3 (15%)	21 (25.9%)
Pain	1 (5%)	3 (3.7%)
Lump and pain	15 (75%)	49 (60.5%)
Nipple discharge	1 (5%)	7 (8.6%)
Skin changes	6 (30%)	18 (22.2%)
Fistula formation	1 (5%)	1 (1.2%)
Lactation within past 6 months		
Yes	3 (15%)	7 (8.6%)
No	17 (85%)	74 (91.3%)
Focality		
Unifocal	14 (70%)	57 (70.4%)
Multifocal	6 (30%)	24 (29.6%)
Duration of symptoms (days)		
Mean	35.7 (1–180)	34.6 (1–270)
Median	21	21
Size of lesion (mm)		
Mean	53.1 (11–113)	45.2 (6–114)
Median	47	46
Bacterial cultures performed	17(85%)	45 (55.6%)
Positive cultures	4 (23.5%)	9 (9.7%)
Corynebacterium	4 (100%)	7 (8.6%)
Staph aureus	0	2 (2.5%)
Initial treatment modality		
Antibiotics	19 (95%)	60 (74.1%)
Prednisolone	16 (80%)	57 (70.3%)
Methotrexate	1 (5%)	0
Surgery	6 (30%)	18 (22.2%)
Observation	0	5 (6.2%)
Duration of treatment		
Antibiotics		
Mean (weeks)	5.2 (1–22)	3.35 (1–15)
Median (weeks)	4	2
Prednisolone		
Mean (weeks)	22.6 (10–72)	16.4 (6–64)
Median (weeks)	20	13

masses without skin changes during their recurrence. One patient was still undergoing treatment with steroids for unresolved recurrence, and four patients (20%) were lost to follow-up.

Discussion

The treatment of GM is frequently complicated by difficulty in recognizing and diagnosing the disease, lack of an optimal treatment modality, prolonged treatment durations and high recurrence rates.

In our series, most patients received antibiotic and steroid therapy. As many patients exhibit inflammatory symptoms and signs, antibiotics are frequently started at presentation. Patients may go through multiple courses of different antibiotics due to unresolving symptoms before GM is eventually diagnosed via CNB or surgery. 87% of patients who received surgical treatment had failure of medical therapy. In our series, all patients who were treated with steroids only achieved resolution but only 9 of 17 patients who received antibiotics only achieved resolution (52.9%); out of which four developed recurrence. This suggests steroid therapy might be a more efficacious mode of treatment than antibiotics.

We examined factors that could have contributed to recurrence in the 20 patients affected. Most of the patients (75%) were presented with signs and symptoms of inflammation. Six patients had surgical excision for their first episode of GM, suggesting that it does not prevent recurrence despite extirpation of the lesion. We were unable to establish statistical significance for various clinical and treatment factors that led to recurrence but found certain factors that contribute to higher odds of recurrence in our patients. Presenting with or receiving treatment due to signs and symptoms of inflammation conferred increased risk of recurrence (in terms of OR): skin changes (1.50), pain (2.00), fistula (4.39) and antibiotic treatment (6.65). Patients with *Corynebacterium* infection had a 2.64 times increased risk of developing recurrence. As the univariate regression did not show statistical significance, multiple logistic regression was not performed. However, our results suggest that a larger sample size in a prospective study might lead to meaningful inference on the primary outcome.

The increased risk of recurrence in patients with inflammatory changes could be due to delay in treatment from initial misdiagnosis as bacterial mastitis or abscess. Florid manifestation of inflammatory signs and symptoms could also represent more chronic and active autoimmune response, and such patients should be closely monitored after initial resolution. In a multicentre study by Uysal et al., breast infection was similarly found to be a risk factor for recurrence of GM [52].

All seven patients with recurrent GM who resolved with observation only presented with painless breast masses. The seven non-recurrent patients treated with only observation, likewise, did not have inflammatory signs and

Table 3 Univariate analysis of factors associated with recurrence of granulomatous mastitis

Variables	Odds ratio (OR)	Confidence interval (CI)	*p* value
Lactation	1.840	0.431–7.860	0.410
Symptom—lump	0.720	0.134–3.867	0.702
Symptom—pain	2.000	0.609–6.568	0.253
Symptom—skin changes	1.500	0.504–4.463	0.466
Symptom—fistula	4.389	0.579–33.274	0.152
Duration of symptoms	1.001	0.989–1.012	0.918
Focality	1.018	0.350–2.964	0.974
Size of lesion	1.006	0.991–1.022	0.424
Culture result	1.108	0.295–4.153	0.879
Corynebacterium positivity	2.643	0.691–10.114	0.156
Treatment—antibiotics	6.650	0.838–52.773	0.073
Treatment—steroids	1.263	0.413–3.867	0.682
Treatment—surgery	1.500	0.504–4.463	0.466
Duration of treatment—antibiotics	1.094	0.970–1.234	0.145
Duration of treatment—steroids	1.007	0.973–1.041	0.705
Time to resolution	1.001	0.999–1.002	0.380

symptoms. This suggests that a lack of inflammatory changes could reflect a lower grade inflammatory process. Observation might be possible in these patients due to eventual "burning out" of this low-grade inflammatory process.

Despite having the largest number of GM patients from a single centre and one of the largest patient numbers in the current literature, our study suffers from limitations common to several of the largely retrospective studies conducted on GM so far. There was wide treatment variability between patients from the lack of a universally agreed treatment algorithm and varying presentations. Due to the long treatment period, some patients defaulted so there could be more patients who recurred but were lost to follow-up. Like a similarly large study examining recurrence of GM, we have found that clinical features of inflammation seem to predispose to recurrence. In addition, we found the presence of *Corynebacterium* infection to have a possible link to recurrence. Analysis of antibiotic susceptibility profile of *Corynebacterium* in our patients showed resistance to penicillin in 7 of 10 (70%) bacterial culture results. Only one of eight (12.5%) cases where sensitivity to clindamycin was tested showed resistance. Penicillins are typically started for GM patients presenting with inflammatory changes to treat presumed gram-positive skin organisms. The high level of penicillin resistance compared to clindamycin in *Corynebacterium* in our patients suggests that non-penicillins might be a better choice of empirical antibiotics in patients with suspected GM. There are no other studies reporting antibiotic susceptibility of *Corynebacterium* in GM patients so far. As more studies are conducted looking at *Corynebacterium* as an aetiologic factor, it might be worthwhile to examine its antibiotic susceptibility as this could lead to more effective initial treatment.

In the light of our findings, we suggest initiating a non-penicillin antibiotic, e.g. clindamycin in patients with suspected GM until antibiotic susceptibility profiles are available. Upon confirmation of GM on histology, preferably obtained through CNB, oral steroid therapy should be initiated with surgery reserved for cases that fail medical therapy. Patients presenting with inflammatory changes have a higher risk of recurrence and should be monitored closely even after resolution of GM.

Despite being a benign disease, the lack of effective treatment regimens and preponderance to recurrence makes GM particularly troubling for those afflicted. Due to the rarity of GM, multicentre prospective studies with larger pooled patient numbers would be useful in furthering our understanding of this disease and how to best treat it.

Compliance with ethical standards

Conflicts of interest The authors report no conflict of interest relevant to this study.

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