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The therapeutic dilemma of idiopathic granulomatous mastitis

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ABSTRACT

Introduction: Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic breast condition that can cause repeated abscesses or mass formation in bilateral breasts. The condition can severely impact the quality of life of affected women. This study aims to evaluate effective treatment modalities, as well as understand the demographics and clinical presentation of patients with IGM.

Methods: An 11-year retrospective review was performed of patients diagnosed with IGM from 1 January 2008 to 31 December 2018 at a tertiary breast unit.

Results: A total of 77 patients were included in the study. The median age at presentation was 36 years old. IGM presented most commonly as a breast lump (98.1%). The median number of flares was 2 (1–12). Of the 77 patients, 68.8% (53) were treated with antibiotics, 50.6% (39) with steroids, and 44.2% (34) underwent surgery, in the course of their IGM treatment. Forty-five (59.2%) of the 76 patients with IGM required a multimodal treatment approach to achieve remission. There was no significant difference in the number of flares no matter the initial treatment (P=0.411), or subsequent treatment modality (P=0.343). Smokers had 10 times greater odds of having a "high flare" of IGM compared to those who did not smoke (P=0.031, odds ratio 10.444, 95% confidence interval 1.092–99.859).

Conclusion: IGM is a clinical diagnosis. It is a rare, relapsing breast inflammatory condition that affects young females with no superior treatment modality. Smoking is associated with higher number of flares of IGM and should be discouraged in IGM patients.

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Keywords: Breast inflammation, chronic mastitis, idiopathic granulomatous mastitis, recurrent breast abscess

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, benign, inflammatory breast condition that can cause repeated abscess or mass formation in bilateral breasts. It has a reported incidence of 2.4 per 100,000 women aged 20–40 years old.[1] Its aetiology is unclear, but various theories have been postulated, including autoimmune, inflammatory and hormonal causes.[2]

It is known to affect largely women of childbearing age (27–38 years old). Studies report up to 100% of patients presenting with palpable masses.[3] Patients may also present with breast pain, erythema, fistulae and ulceration.[1,4,5] IGM represents a diagnostic and therapeutic dilemma, as it mimics breast cancer and infectious mastitis clinically and radiologically. Diagnosis and management of the IGM may be delayed, as it is often a diagnosis of exclusion.[6]

IGM is known to recur frequently, with reported rates of 5–78% of IGM patients having at least 2 flares.[4,7] The protracted course of the disease has a significant effect on the quality of life for these women.[1]

Varied treatment modalities and successes have been reported, with no clearly superior management. The most common treatment options include antibiotics[8] and steroids.[3,5,9] Surgical options such as excisions, incision and drainage, and mastectomies have been performed,[10,11] while successful results with steroids and immunomodulators (such as azathioprine or methotrexate),[12] and observation[10] have been described.

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CLINICAL IMPACT

What is New

- Smoking increases the odds of having a high relapse of IGM by 10 times.
- There is no superior treatment modality for idiopathic granulomatous mastitis.

Clinical Implications

- This study demonstrates how idiopathic granulomatous mastitis is a clinical diagnosis. It should be considered when a young woman has 2 or more episodes of waxing and waning breast inflammation or breast lumps, in spite of treatment instituted.
- Women with IGM should be discouraged from smoking.

METHODS

This is a retrospective review in a tertiary breast unit in an Asian population. All patients diagnosed with granulomatous mastitis from 1 January 2008 to 31 December 2018 at the Breast Unit at Tan Tock Seng Hospital, a tertiary hospital in Singapore, were evaluated. A review of all patients with the histological diagnosis of "granulomatous mastitis", "xanthogranulomatous inflammation", "granulation inflammation", "inflamed granulation tissue", "chronic inflammation" and "granuloma" was also performed to evaluate for suitability for the study.

The clinical diagnosis of idiopathic granulomatous mastitis was based on recurrent inflammation of the breast in the absence of trauma, tumour and tuberculosis. These were guided by the clinical history, breast imaging results and histology report, if present.

Inclusion criteria were women diagnosed with an idiopathic cause of granulomatous mastitis. Exclusion criteria were other causes of granulomatous mastitis such as tuberculosis and foreign bodies. Periodic acid-Schiff stain and/or Grocott's methenamine silver stain were used to detect fungi on histology, while the Ziehl-Neelson stain was used to identify acid-fast bacilli. Demographic profile, histology results, treatment and recurrence rates were documented and evaluated.

Prednisolone was the steroidal agent used. Immunomodulators, where used, included azathioprine or methotrexate. Surgeries included incision and drainage, excision biopsy and mastectomy.

Any flare of IGM during, or after treatment, was considered a failure. A patient was determined to be in the "high flare" group with a high number of recurrences if she had 3 or more flares of IGM, and in "low flare" group if she had 2 or less flares of IGM. This was based on the mean of 2.3 flares in literature.[6] Patients were deemed "super-relapsers" if they were outliers who had more than 6 IGM flares.

This study aims to evaluate effective treatment modalities for IGM. The secondary aim is to understand the clinical presentation and demographics of patients with IGM.

The chi-square test, t-test, and one-way analysis of variance (ANOVA) were used as appropriate. Univariate analyses were performed with Graphpad Prism version 7 (GraphPad software Inc, San Diego, US). P values <0.05 were taken to be statistically significant. Ethics committee approval was granted by the National Healthcare Group Doman Specific Review Board (DSRB 2018/01157).

RESULTS

A total of 77 women were diagnosed with IGM in the Breast Unit at Tan Tock Seng Hospital over 11 years. The median follow-up was 18 (1–131) months.

The median age of the women was 36 (24–84) years. The racial distribution of the women was 57.1% Chinese, 29.9% Malay, 5.2% Indian and 7.8% other races (Table 1); 84.3% were parous. In 32 women with documented age of final pregnancy, the median time from pregnancy to onset of IGM was 4 years (1–28). Of the 77 IGM patients, 75.4% had breastfed previously, while 93.1% had never taken oral contraceptives. Prolactin levels were checked in 8 women; 3 women had hyperprolactinaemia, 2 of whom had pituitary adenomas.

There was a median of 2 flares (1–12) of IGM. IGM presented most commonly as a breast lump in 76 out of 77 patients (98.7%). The working diagnosis at presentation was breast cancer (36.4%) and breast abscess (36.4%). The initial breast imaging reporting and data system (BI-RADS) was ≥3.0 in 63.6% of patients with IGM. Radiological features described included "ill-defined mass" in 36.4% (28 of 77), "hypoechoic mass" in 61.0% (47 of 77), and "heterogeneous lesion" in 46.8% (36 of 77) of IGM patients.

The median duration to arrive at the diagnosis was 1 month (0.1–73). Seventy-two (93.5%) of the 77 women had histologically proven granulomatous mastitis, with the most common diagnosis being granulomatous inflammation (47.4%). Figs. 1 and 2 show characteristic histological findings of patients in the study.

The majority (65.2%) of breast tissue or pus cultured were sterile. The most common organism grown was *Corynebacterium*, found in 15.2% of patients (Table 1).

Steroids were used in the course of IGM treatment in 50.6% of patients (39 of 77), antibiotics in 68.8% (53 of 77), and surgery was performed in 44.2% (34 of 77). The median number of recurrences after initial

Table 1. Characteristics of patients with granulomatous mastitis

Median age (range), years	36 (24–84)
Mean age, years	38
Menopausal status, no. (%)	
No	66 (85.7)
Yes	11 (14.3)
Race, no. (%)	
Chinese	44 (57.1)
Malay	23 (29.9)
Indian	4 (5.2)
Others	6 (7.8)
Comorbidities, no.	
None	45
Diabetes	5
Hypertension	7
Asthma	2
Hyperlipidaemia	5
Psychiatric disorder	7
Others	10
Immunosuppressed, no. (%)	
Yes	4 (5.2)
No	73 (94.8)
Gave birth previously (n=70), no. (%)	
Yes	59 (84.3)
No	11 (15.7)
Oral contraceptive use (n=72), no. (%)	
Yes	5 (6.9)
No	67 (93.1)
Breastfeeding (n=61), no. (%)	
Yes	46 (75.4)
No	15 (24.6)
Obese (n=47), no. (%)	
BMI>25	14 (29.8)
BMI<25	33 (70.2)
Smoking (n=70), no. (%)	
Yes	5 (7.1)
No	65 (92.9)
Presenting complaint, no. (%)	
Breast lump	48 (62.3)
Breast pain	1 (1.3)
Painful breast lump	28 (36.4)
Initial diagnosis, no. (%)	
Breast cancer	28 (36.4)
Breast abscess	28 (36.4)
Granulomatous mastitis	4 (5.2)
Breast lump	6 (7.8)
Abscess vs cancer	11 (14.3)
Initial BI-RADS, no. (%)	
1	1 (1.3)
2	27 (35.1)
3	22 (28.6)
4	20 (26.0)
5	7 (9.1)
Median duration before diagnosis (range), month	1 (0–73)
Histology-proven GM, no. (%)	
Yes	72 (93.5)
No	5 (6.5)
Histology (n=76), no. (%)	
• Acute on chronic inflammation, no granulomas	4 (5.3)
• Acute on chronic inflammation with granulomatous component	15 (19.7)
• Granulation tissue with granulomas	5 (6.6)
• Granuloma	2 (2.6)
• Granulomatous inflammation	36 (47.4)
• Granulomatous mastitis	10 (13.2)
• Xanthogranulomatous inflammation	4 (5.3)
Microorganisms cultured (n=46), no. (%)	
No bacterial growth	30 (65.2)
Corynebacterium	7 (15.2)
Prevotella	1 (2.2)
Proteus	1 (2.2)
Bacillus	1 (2.2)
Staphylococcus	6 (13.0)
Median number of flares (range)	2 (1–12)
Initial treatment, no. (%)	
Antibiotics	43 (55.8)
Steroids	15 (19.5)
Observation	11 (14.3)
Surgery	7 (9.1)
Defaulted	1 (1.3)
Used steroids in treatment, no. (%)	
Yes	39 (50.6)
No	38 (49.4)
Median number of flares after initiating steroids (range)	1 (0–7)
Surgery as part of treatment, no. (%)	
Yes	34 (44.2)
No	43 (55.8)
Median number of flares after initial surgery (range)	1 (0–11)
Used antibiotics in treatment, no. (%)	
Yes	53 (68.8)
No	24 (31.2)
Median number of flares after initial antibiotics (range)	1 (0–11)
Treatment before remission (n=76), no. (%)	
Antibiotics	9 (11.8)
Steroids	28 (36.8)
Steroids with immunomodulators	5 (6.6)
Observation	12 (15.8)
Surgery	21 (27.6)
Surgery and steroids	1 (1.3)
Defaulted treatment	1 (1.3)

BMI: Body mass index, BI-RADS: breast imaging reporting and data system

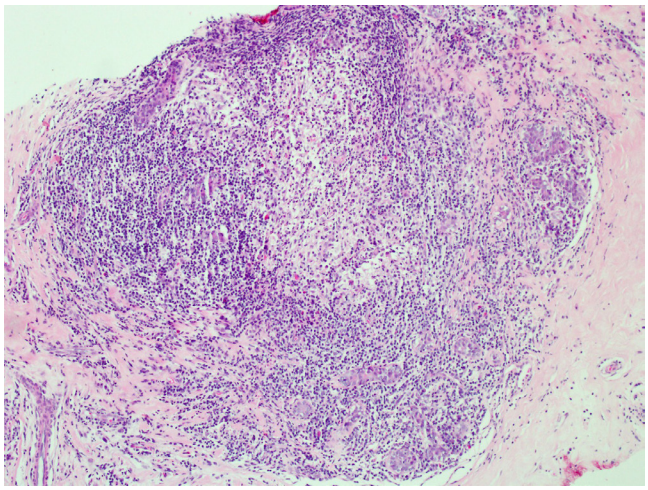

Fig. 1. Breast tissue showing a lobular-centric inflammatory infiltrate, with a granulomatous component. (Haematoxylin and eosin stain, magnification 100x)

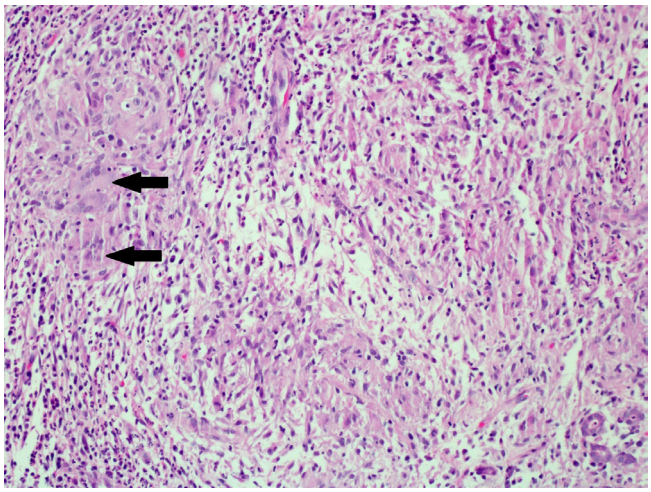

Fig. 2. High power view of the aggregates of epithelioid histiocytes forming granulomas. Multinucleated giant cells are present (arrows). (Haematoxylin and eosin stain, magnification 200x)

treatment was 1, no matter the treatment modality, and there was no statistical significance (P=0.411).

Forty-three of 77 patients (55.8%) were initially treated for a breast infection with oral antibiotics. Of these, 30.2% (13 of 43) resolved without further treatment after a median duration of 16.1 (11.6–37.9) weeks. However, 69.8% (30 of 43 patients) failed to resolve with antibiotics and an alternative treatment was initiated after a median interval of 6.3 (1–319.6) weeks. There was no significant difference in flares between patients who had positive cultures and those with sterile cultures, both of whom received antibiotics (P=0.099).

Fifteen (19.5%) patients were started on steroids as initial treatment. Of these, 12 (80.0%) resolved without further treatment after a median duration of 13.2 (6–47) weeks. Three of the 15 patients with initial treatment of steroids did not respond well, with 1 proceeding with surgery, and 2 requiring immunomodulators after a median duration of 36.6 weeks of steroid treatment. Of all the 77 patients, 24 (31.2%) eventually received steroids after failure of other initial treatment modalities (21 after initial antibiotics, 1 after observation and 2 after surgery). There was no significant difference in the relapse rates of IGM in relation to when steroids were started (whether early in the disease, or after 2 flares) (P=0.827).

The dosing schedule was varied, but with majority starting at 60mg prednisolone daily on tailing dose (ranging from 5mg to 90mg daily). Twenty-five of the 39 patients who received steroids in the course of IGM treatment successfully achieved remission on prednisolone, with 15 (38.5%) requiring only 1 cycle of tailing high dose prednisolone. The median duration of steroid treatment was 14.4 (4.0–62.0) weeks. Eight had a flare of IGM on tailing dose of steroids, with subsequent remission.

Seven (9.1%) patients with IGM had an initial treatment of surgery—5 incision and drainages for an initial diagnosis of breast abscess and 2 excision biopsies for removal of new breast lump. Two of these 7 patients (28.6%) had a remission with surgery alone. Majority of IGM patients with initial surgery required further treatment with steroids, antibiotics or further surgery. A total of 34 (44.2%) IGM patients eventually received surgery, with 13 achieving remission after 1 surgery. There were no characteristics in the surgery or steroid groups, which affected the occurrence of a relapse.

The initial BI-RADS score of the IGM patients who resolved spontaneously without any treatment was higher than those who required treatment (P=0.039). There were no other distinguishing characteristics such as patient demographics or initial working diagnosis.

Follow-up

The median follow-up period was 18 (1–131) months. Fifteen (19.5%) of the 77 patients defaulted follow-up. A significant proportion of these were domestic helpers who were in the country on work visas, and were sent back to their home countries. Others felt symptomatically better and declined return clinic reviews.

Of the 31 (40.8%) patients who received only a single modality of treatment, 17 had no further flares. Being in the high flare group (flare of ≥3 times) was 8-fold

higher when requiring multimodal treatment (*P*=0.003, odds ratio [OR] 7.710, 95% confidence interval [CI] 2.025–29.350).

Forty-five (59.2%) of 76 patients with IGM required a multimodal treatment approach to achieve remission. The main modality to achieve final remission was surgery in 44.4% of patients, followed by steroids in 37.8% of patients.

In 25 patients in the high flare group, the final modality to achieve complete remission was steroidal treatment in 10, steroids and immunomodulators in 5, antibiotics in 1, and surgery for 9 patients. The demographics of the high flare and low flare group were largely similar (Table 2). There is a 10-fold increased odds of smokers having a high number of IGM flares (*P*=0.031, OR 10.444, 95% CI 1.092–99.859). There was no

Table 2. Comparison of characteristics of patients with high flares and low flares

	High flare (n=25)	**Low flare (n=52)**	***P* value**
Median age (range), years	36 (25–53)	36 (24–84)	0.550
Mean age, years	37.3	38.9	
Menopausal status, no.			0.692
No	22	44	
Yes	3	8	
Race, no. (%)			0.362
Chinese	16 (64.0)	28 (53.8)	
Malay	6 (24.0)	17 (32.7)	
Indian	1 (4.0)	3 (5.8)	
Others	2 (8.0)	4 (7.7)	
Comorbidities, no.			0.450
None	13	32	
Diabetes	4	1	
Hypertension	2	3	
Asthma	2	0	
Hyperlipidaemia	1	2	
Psychiatric disorder	1	6	
Others	2	6	
Immunosuppressed, no.			0.098
Yes	3	1	
No	22	51	
Gave birth previously (n=70), no.			0.274
Yes	15	44	
No	5	6	
Oral contraceptive use (n=72), no.			0.163
Yes	3	2	
No	19	48	
Breastfeeding (n=66), no.			0.772
Yes	14	32	
No	5	15	
Obese (n=47), no.			0.344
BMI>25	15	18	
BMI<25	4	10	
Smoking (n=70), no. (%)			0.031
Yes	4 (18.2)	1 (2.1)	
No	18 (81.8)	47 (97.9)	
Initial BI-RADS, no.			0.192
1	1	0	
2	11	16	
3	7	15	
4	4	16	
5	2	5	

BMI: body mass index; BI-RADS: breast imaging reporting and data system

significant difference in the number of flares after steroids, steroids with immunomodulators, or surgery, were commenced (P=0.343).

Fig. 3 shows the Kaplan-Meier curve demonstrating no difference in IGM flare over time, no matter the initial treatment received (P=0.835), nor the specific type of treatment modality received throughout their IGM course (P=0.534) (Fig. 4).

Six patients were super-relapsers, outliers who had 6–12 IGM flares. All of them required multimodality treatment, involving a combination of antibiotics, steroids, surgery and immunomodulators. Three of the 6 patients received immunomodulators. The median number of flares after commencing immunomodulators was 3. One patient even requested for and underwent a bilateral mastectomy, as she was unable to tolerate the recurrent IGM flares.

It took a median of 77 (8–2,237) days to achieve the diagnosis of IGM for super-relapsers, compared to the group within the normal distribution taking 35 (0–544) days (P=0.0001). The super-relapser group was also found to have a lower rate of histology-proven IGM (66.7%), compared to 95.8% in the other group (P=0.006). This is despite all patients in the super-relapser group having had biopsies taken for histology.

DISCUSSION

IGM is a rare inflammatory condition affecting the breast. Only 77 cases were diagnosed in a single tertiary breast centre over 11 years. It largely affected women in their reproductive years, at a median age of 36, in keeping with the literature.[13]

When investigated for microorganisms, 65.2% of patients had a sterile culture, while 15.2% had *Corynebacterium* growth, similar to previous studies.[1,14] The diagnosis of IGM should be considered in recurrent breast abscesses if cultures are sterile, or show *Corynebacterium* growth.

A differential racial representation of IGM incidence has been described, with a higher incidence in Asians, Turkish, Hispanics and Far Eastern populations.[4,15-17] The population of Singapore is made up of 13.4% Malays and 74.3% Chinese.[18] In contrast, a higher proportion of Malay women (29.9%) and lower number of Chinese women (57.1%) were noted to have IGM. Malay women may trend towards an increased likelihood of IGM than Chinese women.

The high flare and low flare groups were largely similar (Table 2), apart from smoking as a risk factor. Our results revealed a 10-fold increased odds of smokers having a high number of IGM flares (P=0.031). This is in keeping with other studies,[4,19] which also reported smoking as a risk factor for IGM recurrence. One in 25 women (4.8%) in Singapore are daily smokers, with a trend towards the tobacco industry targeting women as potential customers.[20] Smoking has been linked with promoting autoimmune diseases such as rheumatoid arthritis by releasing intracellular proteins from reactive oxygen species activated or injured cells, altered presentation of antigens by cigarette smoke-impaired antigen-presenting cells, and altered regulatory B and T cell functions.[21-23] Smoking is also a known risk factor for recurrent breast abscesses and mammillary fistulae.[24] Smoking should be discouraged in women with IGM.

IGM patients in the low flare group tended to only require a single modality of treatment in comparison to the high flare group (P=0.003). It is possible that the clinical course of those with a low chance of recurrence is inherently milder and will likely get better spontaneously, in spite of the treatment administered. Unlike other studies, we did not find parity, breastfeeding or breast infection to be risk factors for IGM recurrences.[4]

Unfortunately, there is a high flare group of patients in whom there will be recurrent flares of IGM. In our patients, 63.6% had at least 2 flares of IGM, compared to 78% of patients in Néel et al.'s study;[2] 32.5% of our patients with IGM had 3 or more flares. Oftentimes, a single modality of treatment may not be sufficient and they will proceed to have a multimodal approach. IGM has a significant but deleterious impact on these patients' quality of life.[1] We noted 1 woman in our study who tried every modality of treatment—antibiotics, steroids, immunomodulators, incision and drainage—but still had 6 recurrences. She ultimately chose to undergo bilateral mastectomy.

The diagnosis of IGM was delayed significantly in the super-relapser group, possibly attributed to the lack of histology to prove IGM. While there was no significant difference in the treatment received, recognition of IGM may help to pace the expectation of the clinical course of IGM for both patients and physician. The subsequent follow-ups, investigations and treatment modalities may also be better tailored for patients with IGM.

The diagnosis of IGM is, ultimately, a clinical diagnosis. IGM should be considered when a young woman has 2 or more episodes of waxing and waning

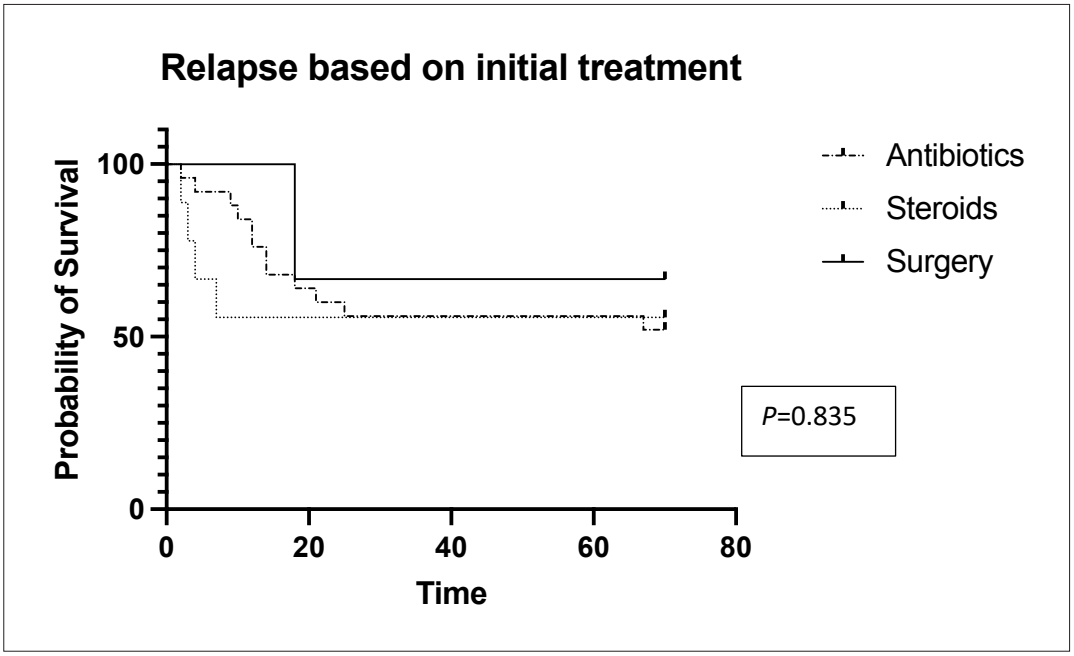

Fig. 3. Kaplan-Meier curve demonstrating relapse over time, based on the initial treatment received.

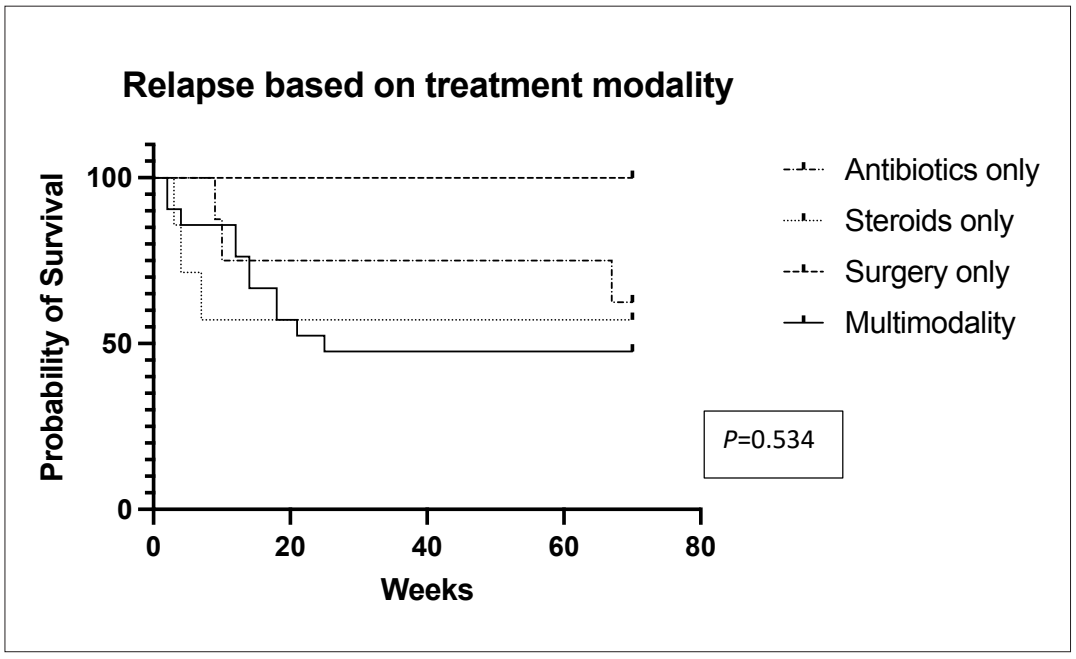

Fig. 4. Kaplan-Meier curve demonstrating relapse over time, based on the treatment received.

breast inflammation or breast lumps, in spite of treatment instituted. A negative histology for IGM does not rule out the diagnosis of IGM.

Literature has no clear consensus on a superior modality of treatment for IGM remission.[4,7] The results of our study support this, revealing no significant difference in the number of flares of IGM whatever the initial modality of treatment (P=0.411). Even in the group with a high number of IGM flares, the type of treatment modality did not affect recurrence or remission (P=0.343). Martinez et al., who published the largest study to date on IGM with 3,060 patients in a systematic review did not observe a correlation between treatment methods and IGM recurrence.[4]

Study limitations

Some patients were lost to follow-up, either because of clinical improvement, or because of return to home countries in the case of foreign workers. As this was a retrospective study, there was no standardised approach among the different surgeons treating IGM patients, which may result in selection bias. As IGM is a rare condition, the number of patients in the current study was small. A multicentre study may be required to further validate the findings of this study.

CONCLUSION

IGM is a clinical diagnosis and there is no superior treatment modality in preventing its recurrence. Smoking is associated with a higher risk of IGM recurrence.

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