Idiopathic granulomatous mastitis in pregnancy: a case report on a new management approach using azathioprine and allopurinol

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Background: Idiopathic granulomatous mastitis (IGM) is a rare, benign inflammatory disease of the breast and is known to have a strong association with pregnancy and lactation. Diagnosing IGM can be delayed as it is often mistaken for infection leading to a period of ineffective antibiotic therapy which defers the appropriate treatment. A differential diagnosis of IGM should be considered in all inflammatory breast masses that have an atypical presentation (large solid component, sinus formation, fistulation, multiple areas) or after a short period of failed empirical antibiotic therapy (1–2 weeks). Core biopsy should be taken at an early stage to rule out neoplasm and confirm the diagnosis of IGM. IGM is characterised histologically by non-caseating lobulocentric granulomatous inflammation. The presence of the *Corynebacterium kroppenstedtii* bacterium is widely associated with the onset of IGM. There is a lack of consensus for optimal treatment for IGM which can make this condition challenging for clinicians to manage. The management of IGM should follow a multi-disciplinary approach.

Case Description: We report a case of a 31-year-old woman with IGM refractory to steroid treatment whose disease was successfully treated and kept in remission during a subsequent pregnancy using a new regimen of azathioprine and allopurinol. This case highlights the challenges in diagnosing and treating IGM; a condition commonly associated with prolonged suboptimal management with extended antibiotic and glucocorticoid therapy as well as limited treatment options for women who are pregnant and/or breastfeeding.

Conclusions: This case has guided the development of a new complex breast abscess and IGM treatment algorithm to guide management in all women including those in the pregnancy and post-partum period. It involves a multidisciplinary team approach and is a useful tool to clinicians in ensuring prompt diagnosis, targeted therapy and the avoidance of unnecessary operative management.

Keywords: Idiopathic granulomatous mastitis (IGM); complex breast abscess; breast disease in pregnancy; breast abscess pathway; case report

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rare, benign inflammatory disease of the breast (1). It is characterised histologically by non-caseating lobulocentric granulomatous inflammation and usually affects one side only (2). It is commonly seen in women of child-bearing age and is known to have a strong association with pregnancy and lactation although the exact aetiology is unknown (2,3). The clinical presentation includes a palpable breast mass with inflammation, skin ulceration, sinus and fistula formation with discharge. Diagnosis can be challenging because the condition is often mistaken for infection and a period of ineffective antibiotic therapy can delay correct treatment. Other diagnoses such as inflammatory breast cancer and systemic inflammatory conditions will need to be ruled out before a formal diagnosis of IGM is established. The *Corynebacterium kroppenstedtii* bacterium is widely associated with the onset of IGM and can be tested for on bacterial cultures. In diagnosing IGM, histological features should include granulomatous inflammation.

There are currently no consensus guidelines for treating IGM and there are few cases published on its management during pregnancy. The most recently published case reports favour oral glucocorticoids and methotrexate as first line treatments but chronic use of both drugs is typically contraindicated in pregnancy and breast-feeding (1,2,4-7). Given the complexities of both diagnosis and management, IGM should ideally be managed via a multi-disciplinary approach (8).

We report a case of IGM in a pregnant woman successfully treated using a new regimen of azathioprine and allopurinol. This has guided the development of a new complex breast abscess pathway involving breast surgeons, gastroenterologists, infectious diseases specialists, radiologists and pathologists to diagnose and manage IGM. We present the following case in accordance with the CARE reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-22-8/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 31-year-old Caucasian female, four months post-partum and actively breast feeding, presented with a 4-week history of a tender left breast mass with overlying skin discolouration. She was previously fit and well, and was a non-smoker with no past medical, drug or family history. She was treated empirically with two consecutive courses of antibiotics (flucloxacillin followed by co-amoxiclav) for presumed lactational mastitis by the general practitioner (GP). Urgent two week wait referral to the breast unit was made on worsening of symptoms and development of a painful fluctuant breast mass which required ultrasound guided drainage. An inflammatory breast cancer was ruled out and the pus culture sample had no growth of bacterial organisms. Co-amoxiclav was continued.

Over the following months her symptoms progressed with features of new ulceration and large volume pustular discharge. She also developed a second inflammatory mass with additional smaller collections and the formation several sinuses. Repeat ultrasound scans were performed with pus aspirations for microscopy and culture (*Figure 1*) which grew *Staphylococcus Aureus* with sensitivity to clindamycin. She was therefore started on clindamycin for 2 weeks. Over the next 6 weeks she continued to develop multiple new areas of ulceration with discharging sinuses. New pus cultures grew *Acinetobacter ursingii* and *Enterobacter faecalis*. Due to the protracted course of the disease at 12 weeks following her initial presentation, the first core biopsy of the breast tissue was performed. This showed lobulocentric inflammation, non-caseating granulomas and microabscesses (*Figure 2*) (9). The mixed inflammatory infiltrate composed of lymphocytes, plasma cells, neutrophils. Special stains for fungal elements (Periodic acid-Shiff diastase) and mycobacteria (Ziehl-Neelsen) were negative. Recommendation from the Breast MDT was to opt for sensitivity-targeted antibiotic therapy management and termination of lactation using cabergoline.

At four months from initial presentation with no symptomatic improvement, a diagnosis of presumed IGM was made. Referral to the Infectious Diseases Unit to rule systemic inflammatory diseases and other infective granulomatous conditions (tuberculosis or complex non-tuberculous mycobacterial infection) was done. Fresh large bore core biopsy samples were taken for prolonged cultures and showed no evidence of mycobacterium infection. Antibiotic therapy was then stopped and daily

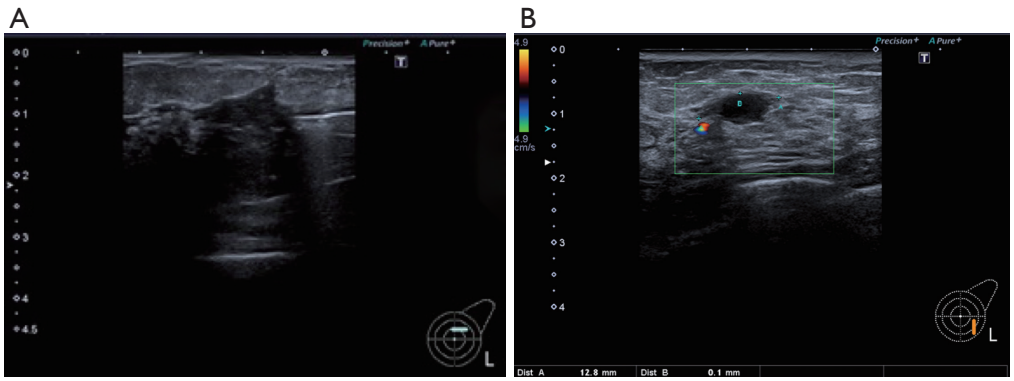

Figure 1 Ultrasound appearance of idiopathic granulomatous mastitis. (A) An area of mixed echogenic change measuring in excess of 40 mm with both solid and fluid components. (B) Hypoechoic area in the skin layer with fistula tracking down to an irregular hypoehoic area with increased vascularity deep within the breast tissue. Surrounding chronic inflammatory changes.

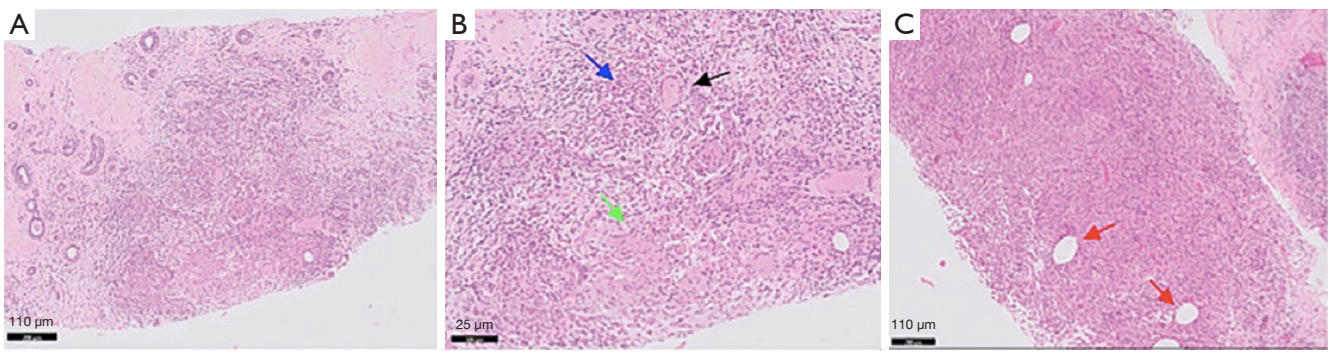

Figure 2 Histological appearance of idiopathic granulomatous mastitis. Staining methods: Haematoxylin and eosin. (A) Mixed inflammation with a lobulocentric distribution composed of histiocytes, multinucleated giant cells, lymphocytes, plasma cells and neutrophil polymorphs. (B) Higher power image showing an epithelioid granuloma (green arrow), micro-abscess (blue arrow) and Langhans' type giant cell (black arrow). (C) A more established focus of inflammation, effacing the lobule with empty spaces representing lipid (red arrows).

oral prednisolone was commenced at 30 mg once daily for four weeks. Almost immediate clinical improvement was seen but it was a challenge in balancing the side effects of the steroids (diarrhoea, abdominal discomfort, weight gain) with the quiescence of symptoms. A reducing dose regimen was commenced with a reduction of prednisolone by 5 mg every week. Unfortunately, her symptoms worsened once the dose of prednisolone went below 10 mg daily and re-initiation of 30 mg prednisolone was required to regain control. Re-evaluation of the most appropriate immunosuppressive regimen was necessary after concerns were raised with steroid dependence, steroid side effects and the planning of a second pregnancy.

Azathioprine has a lower long term side effect profile compared to glucocorticoids and is considered appropriate as a maintenance immunosuppressant (10). It is low risk in pregnancy when deemed clinically necessary unlike methotrexate which is absolutely contraindicated (11). Gastroenterology input was required due to their familiarity of azathioprine and expertise in ruling out IGM as an extra-intestinal manifestation of inflammatory bowel disease (IBD) (normal calprotectin and colonoscopy) and granulomatous hepatitis (normal liver ultrasound scan and serum liver function tests). Given the patient's sub-therapeutic 6-methylmercaptopurine levels on pre-monitoring blood tests, allopurinol 100 mg was given in combination with a lower dose of azathioprine 50 mg. Whilst this combination of drugs has a recognised interaction risk of haematological toxicity, once carefully monitored can have a desired anti-inflammatory effect and low side effect profile (12-14). An

Table 1 Investigations required prior to starting azathioprine to limit side effects (15)

Thiopurine methyltransferase levels
Hepatitis B and C serology
Human immunodeficiency virus
Varicella zoster exposure testing
Chest X-ray (to exclude to previous tuberculosis)
Full blood count
Renal function tests
Liver function tests
QuantiFERON-TB gold
Strongyloides serology

initial short course of tapering 30 mg Prednisolone was re-started whilst azathioprine was titrated into therapeutic range. Response to this new drug regimen showed immediate and significant improvement of inflammation, tenderness and no further discharge from sinuses. Prior to initiation of this regimen, full safety checking to limit side effects to azathioprine was done (*Table 1*) (15).

A year following initiation of treatment the patient had a successful second pregnancy whilst remaining on the same regimen. She reported one minor flare at 19 weeks into pregnancy which was due to reduced compliance with medication and was quickly controlled once recommenced. Otherwise, her disease remained quiescent throughout the pregnancy and into the post-partum period. She had an uncomplicated labour and delivered a healthy baby. Currently at 8 months post-partum, the patient has had no recurrence or relapse of IGM and remains on the same medication with no side effects. She is under surveillance once every four months by the breast and gastroenterology teams. *Figure 3* shows photographic documentation of the clinical course and a detailed timeline can be found in Table S1.

Discussion

IGM is a rare condition with an incidence of 2.4/100,000 (3). Due to the low incidence, published data for this condition exists mainly in the form of retrospective studies and small case series. There is a lack of consensus for optimal treatment which has made this condition challenging for clinicians to manage. The management of IGM using azathioprine in a cross discipline approach has not previously been reported in pregnancy and lactation. Current described treatment regimens include antibiotic therapy, oral corticosteroids, immunosuppressive therapies and surgical intervention (3). Surgical management can range from incision and drainage, excisional biopsy, partial or complete mastectomy to immediate or delayed breast reconstruction (16). A systematic review and meta-analysis performed by Ma *et al.* showed that surgical management was the best and fastest way to complete eradication of IGM for patients not concerned with surgical scarring (17). Breast conserving options such as wide local excision have been associated with a high recurrence rate, delayed wound healing, fistula formation, extensive scarring and poor cosmesis (18). A percentage of these patients will then require concurrent steroid therapy. The option of surgical management is also limited in pregnancy.

Early presentation mimics infective conditions such as mastitis and breast abscess and diagnosis is therefore often delayed while empirical antibiotic therapy is commenced. Antibiotics have shown relatively low success rates (6–21% clinical improvement) as IGM is classically a non-infective inflammatory condition; however, there are cases with superimposed infection, as demonstrated in this patient, in which they can be beneficial (3). While needle aspiration for microbiology is common practice to rule out infection, taking core biopsies is not. However, histological assessment is usually performed after antimicrobial treatment fails and it becomes necessary to consider alternative diagnoses, including inflammatory breast cancer.

The key histological feature of IGM is granulomatous inflammation centred on the breast lobule (9,19). This spatial relationship with the lobule is less conspicuous in other causes of granulomatous inflammation that may enter the differential diagnosis, such as mammary duct ectasia and sarcoidosis, although the lobule may eventually become destroyed and replaced by sheets of inflammatory cells (9,19,20). In addition to the granulomatous/histiocytic component, which includes Langhans-type giant cells, variable numbers of lymphocytes, plasma cells, eosinophils and neutrophil polymorphs are seen, the latter of which may form microabscesses. Clear spaces thought to represent lipid are sometimes noted within the inflammation or granulomata and histiocytes with cytoplasmic accumulation of lipid may develop a foamy appearance (9). Other features include fat necrosis and ductal inflammation (9,19). It

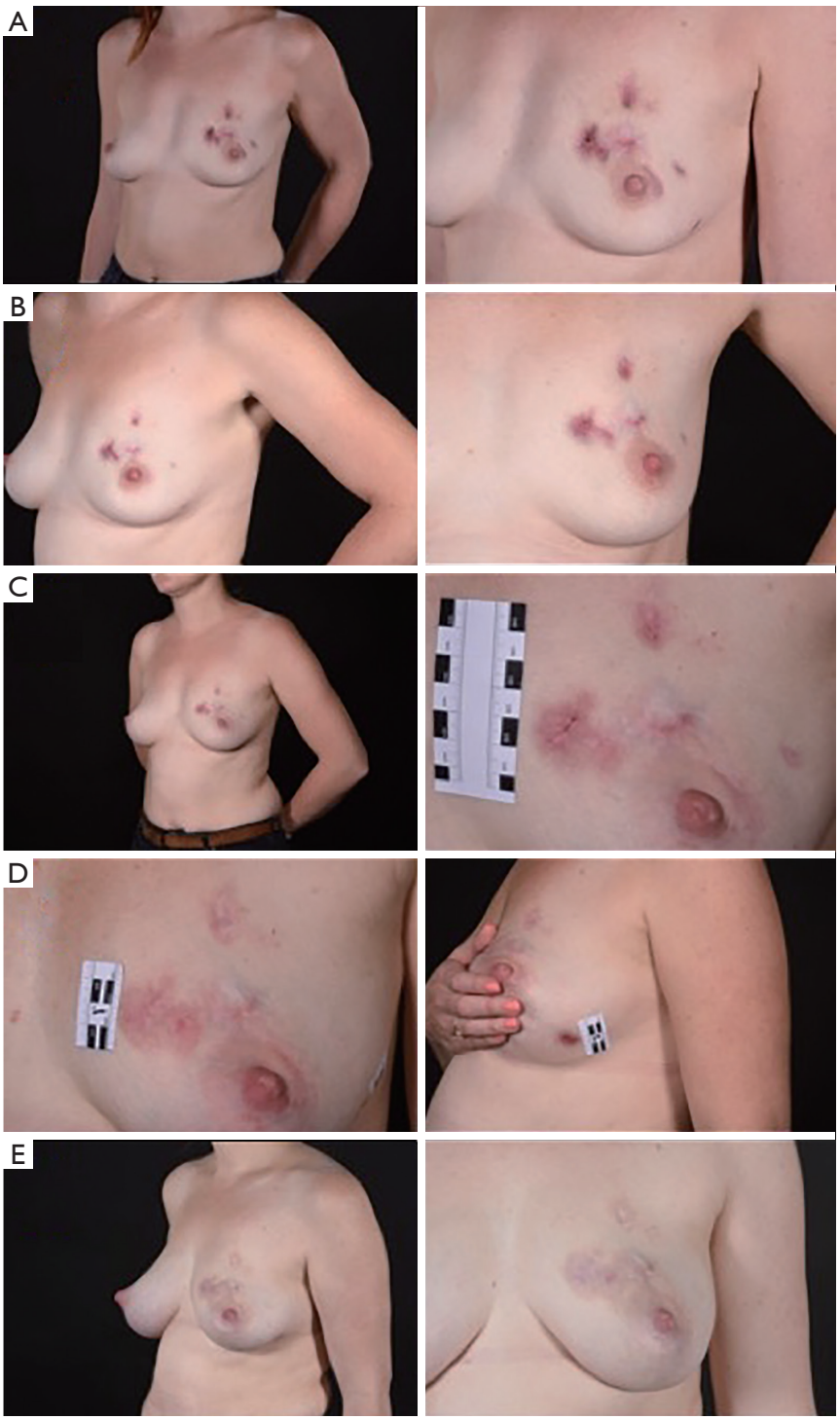

Figure 3 Clinical appearances of IGM. (A) 8 months of intermittent antibiotic therapy prior to formal diagnosis of IGM being made. Showing induration, inflammation, skin breakage and multiple sinuses with underlying fistula tracts. (B) 2 months of prednisolone therapy. Showing improvement of symptoms. (C) 8 months of prednisolone therapy. Showing further improvement of symptoms. (D) Relapse during pregnancy due to poor compliance with medication (azathioprine and allopurinol). Showing induration, inflammation and re-formation of sinus in lower outer quadrant of the breast. (E) 1 month post-partum on azathioprine and allopurinol. Showing quiescent disease. IGM, idiopathic granulomatous mastitis.

Table 2 List of conditions to be excluded to confirm diagnosis of idiopathic granulomatous mastitis (23)

Neoplastic
Inflammatory carcinoma of the breast
Inflammatory
Idiopathic inflammatory mastitis
Infectious
Breast abscess (bacterial or mycobacterial)
Tuberculous mastitis
Histoplasmosis
Autoimmune
Sarcoidosis
Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
Inflammatory bowel disease
Granulomatous hepatitis
Systemic lupus erythematosus
Common variable immunodeficiency
Rheumatoid arthritis
Anti-neutrophil cytoplastic autoantibody vasculitis

has been suggested that ductal damage, due to either inflammation or trauma could be the precipitating event in IGM, with the resultant leakage of secretory material into the stroma initiating the granulomatous response (20).

The *Corynebacterium* species of bacteria is widely detected in granulomatous mastitis but the relationship between them is not yet definitive. Literature indicates a potential causal relationship between cystic neutrophilic granulomatous mastitis (CNGM) and *Corynebacterium*, with *Corynebacterium kroppenstedtii* being the most commonly occurring organism of the species (21). Patients with *Corynebacterium* infections are more likely to present with fever and sinus formation. In such cases, the pathologist should investigate for any primary bacterial infection and consider culture of fresh specimens, gram staining or rRNA gene sequencing of specimens obtained at surgery (22). Early recognition of CNGM may warrant first line treatment with lipophilic antimicrobials such as clindamycin (21).

The diagnosis of IGM is made once all other causes (including all infective, other granulomatous conditions and neoplasm) have been excluded (*Table 2*) (23). Once a diagnosis of IGM is made, most clinicians prescribe short courses of oral glucocorticoids as first-line treatment. Patients generally respond well to glucocorticoids with reported symptom resolution between 66–72% (3). However, once the dose is tapered, the rate of recurrence can be as high as 20% (24). Long courses of corticosteroids are not recommended due to the extensive side effect profile in a relatively young patient cohort. Important side effects include osteoporosis, diabetes mellitus, peptic ulcer disease, significant weight gain, insomnia, avascular necrosis and predisposition to infection. Its use is avoided in pregnancy due to the increased risk of teratogenesis, gestational diabetes, preterm delivery, interaction with obstetric medication (specifically mifepristone) and concerns with hypothalamic-pituitary-adrenal (HPA) axis alteration in neonates (25).

The use of immunosuppressants, particularly methotrexate, as second-line treatment has also been reported in the literature (26). The use of methotrexate in combination with corticosteroids has shown promising results however the efficacy of methotrexate as monotherapy is still largely unknown with only two recently published studies available (27-29). Moreover, the side effect profile of the drug and its absolute contraindication in both pregnancy and breast-feeding render it an unsuitable option for the majority of the IGM patient cohort.

Azathioprine, a thiopurine metabolite, is an alternative immunosuppressant with fewer side effects and can be administered in pregnancy and breast-feeding when clinically deemed necessary (10,11). To date, there are only 5 publications (1 case report and 4 small case series) describing the treatment IGM using azathioprine in combination with glucocorticoids, with no studies describing azathioprine as monotherapy (30-35).

Safe prescription of azathioprine requires pre-treatment drug counselling and attentive therapeutic monitoring (36). Thiopurine methyltransferase (TPMT) levels can be measured to determine a patient's level of risk to myelosuppression before starting treatment and 6-Thioguanine nucleotide (6-TGN) levels to check a therapeutic level of the active metabolite has been achieved. Patients are co-prescribed allopurinol when this has not been achievable and their 6-TGN levels are subtherapeutic, or when they are suspected to have side-effects to high levels of methyl-mercaptopurine. A low dose of allopurinol 100 mg daily is sufficient to induce the noted metabolic switch in this cohort of patients (37).

The dose of azathioprine should be reduced by 25% of the recommended dose and guided with a careful monitoring regimen with regular blood tests (full blood count and liver function tests). Allopurinol acts to inhibit the second step of metabolism of azathioprine to 6-mercaptopurine and can result in higher levels of this which can result in haematological toxicity (38). The white cell count (WCC) should be checked every week for the first 4 weeks after allopurinol is added, then once every fortnight for the next 4 weeks and then once every three months long term. This is to monitor for blood dyscrasias, leukopenia, thrombocytopenia or pancytopenia (38). Metabolite levels should also be checked approximately 4 weeks after starting allopurinol to ensure therapeutic levels have been attained and to allow for further azathioprine dose adjustment if required (37). Increasingly in clinical practice, some patients request an immunosuppressive regimen associated with the lowest probability of side-effects, and this approach of low dose azathioprine with allopurinol can be considered if suitable. This has been shown to be effective and is more tolerable (12-15).

As azathioprine is a drug that is not routinely used by breast surgeons, joint care with another specialty with this expertise is recommended. A small number of publications on IGM management have described adopting such a multidisciplinary approach and usually include collaboration with Rheumatology physicians (38). In this case, the existing expertise that gastroenterologists have using azathioprine to treat patients with IBD led to the establishment of a joint pathway for this patient. There are some similar histological characteristics, including the presence of non-caseating granulomas, shared between IGM and IBD. Reports of patients with both IGM and IBD have described improvements in both conditions when treated with azathioprine (38).

This case highlights the challenges of diagnosing and treating IGM. As with many patients with IGM, there was a prolonged period of suboptimal management with unnecessary extended antibiotic and glucocorticoid therapy. The patient's young age and wish for a second pregnancy was a driving factor to consider other approaches to controlling her disease. Our experience in this case has led to the development of a multidisciplinary approach towards the management of complex breast abscesses involving breast surgeons, radiologists, pathologists, infective diseases specialists and gastroenterologists. This treatment algorithm (*Figure 4*) aims to reduce diagnostic delays and to expedite optimum treatment for all patients with IGM including those who are pregnant or lactating.

The possibility of a diagnosis of IGM should be considered in all inflammatory breast masses that have an atypical presentation (large solid component, sinus formation, fistulation, multiple areas) or after a short period of failed empirical antibiotic therapy (1–2 weeks). Core biopsy at this early stage is recommended for the exclusion of neoplasm, to demonstrate the presence of granulomas and to provide good quality tissue for prolonged microbiology cultures including acid fast bacilli. We recommend that the identification of granulomas on core biopsy leads directly to referral to the infectious diseases team who can perform chest radiographs, QuantiFERON testing, test for sarcoidosis and review of culture and antimicrobial therapy. This stage is important as immunosuppressive therapy for IGM can only be commenced once non-caseating granulomas have been demonstrated and all infective causes have been excluded. This stage, even when expedited could take several weeks. Once the diagnosis of IGM is made, the breast team can safely attempt a single course of oral glucocorticoid therapy. High dose prednisolone can be maintained for 4 weeks once symptoms have resolved and then tapered with a reducing regimen. To avoid long term sequelae from steroid therapy, the aim is to stop steroids completely after the tapering regimen and not to maintain disease control on a low dose of steroid as is the approach with other inflammatory conditions. Disease relapse within 1-year after a single course of steroids, or a relapse while weaning the initial course of steroids should trigger referral a to a specialist with expertise in immunosuppressive therapy to discuss the benefits of steroid sparing treatments such as azathioprine or methotrexate. This could be the rheumatologists or gastroenterologists.

This case demonstrated that long term disease control can be effectively maintained using single immunosuppressive therapy with azathioprine even in pregnancy and whilst breastfeeding. A multidisciplinary approach was important to safely achieve this outcome. She will undergo planned interval azathioprine withdrawal in the future while under joint care of the breast surgeons and gastroenterologists.

Learning points to guide clinicians on the management of IGM can be found in *Table 3* and the patient perspective can be found in Appendix 1.

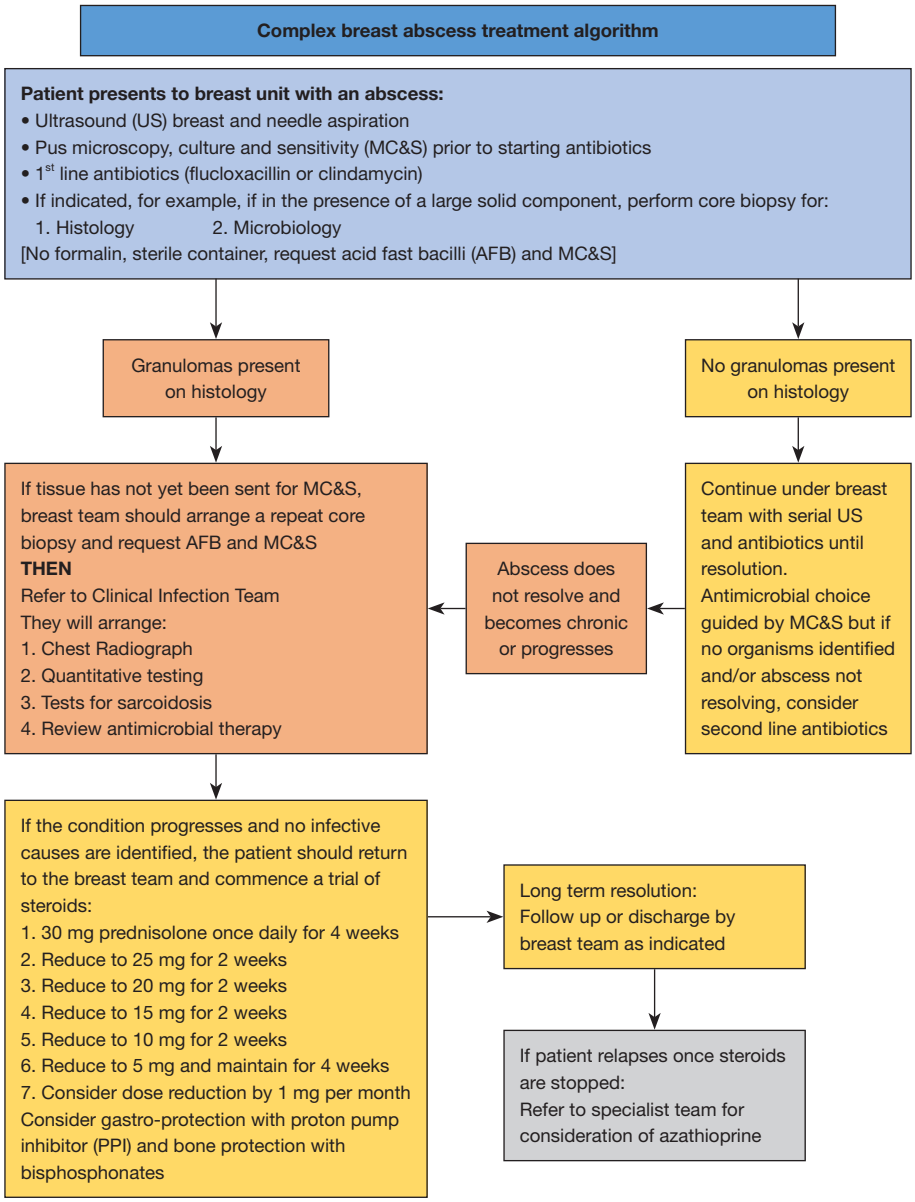

Figure 4 New complex breast abscess & idiopathic granulomatous mastitis treatment algorithm.

Table 3 Learning points

IGM is a rare condition that is difficult to treat due to limited data and lack of treatment consensus
Early core biopsies for microbiology and histology should be performed in inflammatory breast masses with atypical appearances (large solid component, sinus formation or fistulation) or after a short period of failed antimicrobial therapy (1–2 weeks)
A multidisciplinary pathway involving breast surgeons, radiologists, pathologists, infectious diseases specialists and a specialty with expertise in prescribing azathioprine (rheumatology or gastroenterology) is recommended
Azathioprine is effective in IGM including in women who are pregnant and/or breast-feeding
Azathioprine monotherapy avoids the detrimental side effects of long term glucocorticoid use

IGM, idiopathic granulomatous mastitis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-22-8/rc

Peer Review File: Available at https://asj.amegroups.com/article/view/10.21037/asj-22-8/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-22-8/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Supplementary

Table S1 Clinical timeline of a 32-year-old female with delayed diagnosis of IGM

Timeline	Symptoms	Management	Investigations	Results
4 weeks	Tender breast mass with overlying skin discolouration	Empirical antibiotic therapy for suspected lactational mastitis by general practitioner	None	None
		Flucloxacillin followed by co-amoxiclav		
5 weeks	Fluctuant breast mass	2 weeks wait referral to breast surgeons	1st ultrasound guided needle aspiration	MC&S no growth
		Co-amoxiclav continued		
6 weeks	Worsening symptoms with new ulceration and discharge	Sensitivity-targeted antibiotic therapy started	2nd ultrasound guided needle aspiration	Staphylococcus aureus with sensitivity to clindamycin
12 weeks	New second inflammatory mass with ulceration and sinus formation.	Referral to breast MDT meeting	3rd ultrasound guided needle aspiration	MC&S grew *Acinetobacter ursingii & Enterobacter faecalis* with sensitivities
		MDT outcome:	1st core biopsy	Histology showed lobulocentric inflammation, non-caseating granulomas and microabscesses
		1) Ongoing sensitivity targeted antibiotic therapy		
		2) Cabergoline for termination of lactation		
4 months	No symptomatic improvement	Referral to infectious disease unit	Fresh large bore core biopsy samples for prolonged cultures	No evidence of mycobacterium infection such as tuberculosis or complex non-tuberculous mycobacterial infection
	Diagnosis of IGM made	Antibiotics stopped		
		Glucocorticoid therapy started (30 mg prednisolone)		
5 months	Immediate clinical improvement with reduction in pain, inflammation and discharge. Closure of sinuses	Ongoing glucocorticoid therapy with proton pump inhibitor cover and calcium supplements	–	–
6 months	Steroid side effects of weight gain and gastrointestinal symptoms	Gastroenterology input	Azathioprine safety checklist performed (see *Table 1*)	Safe to start azathioprine
	Relapse of IGM symptoms once steroid dose tapered	New regimen started:		
		1) Short course tapering prednisolone		
		2) 50 mg azathioprine		
		3) 100 mg allopurinol		
12 months later and to present date	Complete quiescence of symptoms	Remains on low dose regimen of azathioprine 50 mg and allopurinol 100 mg	Regular monitoring of:	Surveillance once every 4 months with breast surgeons and gastroenterologists
	No side effects		• Full blood count	
	No further flares of IGM		• Liver function tests	
	Successful second pregnancy		• 6-Thioguanine nucleotide	
			• Methyl-mercaptopurine	

IGM, idiopathic granulomatous mastitis; MC&S, microscopy, culture and sensitivity; MDT, multi-disciplinary team.

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Appendix 1 Patient perspective

"It was a long and challenging journey to get to the diagnosis of IGM and since starting the new treatment with azathioprine and allopurinol the disease has been completely under control. I have been able to take both medications throughout a new pregnancy and while breastfeeding with no harm to the baby. Thank you."

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