BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

# An update on granulomatous mastitis: a rare and complex condition

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## Abstract

Granulomatous mastitis is a rare inflammatory condition of the breast affecting women of child-bearing age. The disease is characterised by chronic and relapsing inflammation, resulting in scarring and discharging sinuses. Granulomatous mastitis is considered to be idiopathic and the pathogenesis is poorly understood. An amplified immune response has been proposed as a likely cause and there is evidence linking *Corynebacterium* to some cases of granulomatous mastitis. The presentation is similar to bacterial mastitis or abscess and antibiotics are commonly commenced empirically. The cornerstone of diagnosis is histopathological evaluation on core biopsy; an index of suspicion based on demographic assessment can avoid delays in diagnosis. Management is difficult and there is no consensus on best treatment. Various treatment regimens are described, with high relapse rates relating to the nature of the condition. Watchful waiting is appropriate for mild presentations and steroids are the mainstay of treatment for more severe cases. This article reviews the emerging evidence on granulomatous mastitis and describes an updated approach to management.

**Key words: Breast, Granulomatous mastitis, Idiopathic granulomatous mastitis, Management, Treatment**

**Received: 7 December 2020; accepted following double-blind peer review: 25 January 2021**

## Introduction

Granulomatous mastitis belongs to a group of benign inflammatory conditions resulting in the formation of granulomata seen on histopathological evaluation. Other conditions in which a granulomatous reaction can occur in the breast include systemic autoimmune diseases, and localised infectious and foreign body reactions (Benson and Dumitru, 2016; Barreto et al, 2018; Valente and Grobmyer, 2018). The term granulomatous mastitis was first described in 1972 as an idiopathic condition that mimics breast carcinoma (Kessler and Wolloch, 1972). The natural history is often chronic and relapsing. The rare occurrence of granulomatous mastitis has contributed to poor understanding of aetiology and best management.

## Demographics

Granulomatous mastitis most commonly affects women of child-bearing age (19–49 years) and usually within 5 years of pregnancy (Freeman et al, 2017; Barreto et al, 2018; Valente and Grobmyer, 2018; Martinez-Ramos et al, 2019). The condition is more common in women of Middle Eastern or Hispanic ethnicity (Barreto et al, 2018; Valente and Grobmyer, 2018; Hashmi et al, 2020). Men may also be affected – in a small cohort study (Barreto et al, 2018), 3.4% of those affected were male. In these specific cases there was a history of hormonal manipulation or alteration, suggesting altered hormonal influence as a precipitating factor, such as a transgender person who was taking oestrogen, and another with cryptorchidism which was corrected at a late age.

## Risk factors

Various factors have been identified which predispose to granulomatous mastitis. High oestrogen states such as in pregnancy, high prolactin levels and breastfeeding have been associated with the condition (Taylor et al, 2003; Barreto et al, 2018; Valente and

**How to cite this article:**
Coombe RF, Hamed H. An update on granulomatous mastitis: a rare and complex condition. Br J Hosp Med. 2021. https://doi.org/10.12968/hmed.2020.0718

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Grobmyer, 2018). A history of autoimmune disease and erythema nodosum (hypersensitivity inflammatory disorder of the subcutaneous fat) have been implicated (Cox et al, 2010); a systematic review of 3060 cases of granulomatous mastitis (Martinez-Ramos et al, 2019) reported associations in 34 and 8% respectively. Genetic factors may also be connected, as suggested by the more common presentation in specific ethnic groups (Barreto et al, 2018; Hashmi et al, 2020). Some authors linked the risk to use of the oral contraceptive pill (17–22% of patients) (Barreto et al, 2018) and smoking (Oran et al, 2013), but this association was not found by others (Taylor et al, 2003; Aghajanzadeh et al, 2015; Benson and Dumitru, 2016; Valente and Grobmyer, 2018).

## Aetiology

The exact aetiology of granulomatous mastitis is unknown, and other conditions resulting in granuloma formation in the breast need to be excluded (Table 1) (Valente and Grobmyer, 2018). An amplified immune response has been proposed as a likely cause. The proposed pathway is a local inflammatory event in the way of trauma by chemical irritant, hormonal changes or infection. This causes damaging luminal secretions to come into contact with lobular connective tissue, resulting in an inflammatory response with lymphocyte and macrophage migration and eventual granulomatous response (Valente and Grobmyer, 2018).

## Corynebacterium

Granulomatous mastitis is usually regarded as a sterile process, but there is growing evidence of a link to *Corynebacterium.* The finding was first published in 2002 by a New Zealand group (Paviour et al, 2002; Taylor et al, 2003) and several reports have since followed (Johnson et al, 2016; Johnstone et al, 2017). Taylor et al (2003) retrospectively reviewed cases of granulomatous mastitis where *Corynebacterium* was isolated and concluded the bacterium to be the causative organism in a proportion of cases. Several strains have been isolated, the most common being *Corynebacterium kroppenstedtii* (Taylor et al, 2003; Dobinson et al, 2015; Johnstone et al, 2017). *Corynebacterium* is difficult to see on Gram stain without specific culture medium. The bacterium is part of normal skin flora and in the past, when detected in granulomatous mastitis specimens, it was considered a contaminant rather than a pathogen. It is suggested that it is a cause of infection rather than colonisation or contaminant; in granulomatous mastitis the bacterium is seen deep in the breast tissue away from skin, it is present early on in the disease process and is surrounded by granulomatous inflammation (Johnstone et al, 2017). The connection is now widely accepted and has changed many institutional policies. Where cultures are not successful at isolating the bacterium, 16s RNA gene sequencing and specialised mass spectrometry

**Table 1. Causes of breast granulomata**

| | | |
|---|---|---|
| Infectious | Bacterial | Tuberculosis (*Mycobacterium tuberculosis*), leprosy (*Mycobacterium leprae*), cat scratch disease (*Bartonella henselae*) |
| | Fungal | Histoplasmosis, Cryptococcosis |
| | Protozoal | Schistosomiasis |
| Autoimmune | Vasculitis | Granulomatosis with polyangiitis, giant cell arteritis, Takayasu's arteritis, Churg–Strauss syndrome |
| | Crohn's disease | |
| | Sarcoidosis | |
| Foreign body reaction | Carbon | |
| | Silicon | |
| | Beryllium | |

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(MALDI-TOF MS) can be used to identify its presence (Johnson et al, 2016; Johnstone et al, 2017). A distinct histological pattern is seen associated with *Corynebacterium* termed 'cystic neutrophilic granulomatous mastitis' (Dobinson et al, 2015; Johnstone et al, 2017) which may direct suspicion of this infectious cause.

## Presentation

Granulomatous mastitis usually presents as a tender, palpable, unilateral breast mass with an average size of 5 cm. The overlying skin is erythematous and indurated (Aghajanzadeh et al, 2015; Freeman et al, 2017; Barreto et al, 2018) (Figure 1). The nipple may be retracted as a result of the inflammatory process. It could also present with nipple discharge (Martinez-Ramos et al, 2019). The process can affect any area of the breast (Taylor et al, 2003) and bilateral disease is reported only in 9% of cases (Valente and Grobmyer, 2018). Sinus tract formation with or without suppurative discharge and scarring is a sign of chronic inflammation. Enlarged axilla lymph nodes may be present in up to 40% of presentations (Benson and Dumitru, 2016). Patients with fever, neutrophilia, sinus tract formation and bilateral disease may suggest associated infection caused by *Corynebacterium* (Taylor et al, 2003; Johnstone et al, 2017).

Granulomatous mastitis can present as a diagnostic challenge and, as a result, diagnosis is often delayed by an average of 4–5 months (Martinez-Ramos et al, 2019). It is most often initially misdiagnosed as bacterial mastitis or abscess because of its similar presentation (Table 2). Definitive diagnosis is usually on core biopsy following failed treatment with antibiotics (Valente and Grobmyer, 2018).

**Figure 1.** Relapse of granulomatous mastitis.

**Table 2. Differential diagnosis of granulomatous mastitis**

| |
|---|
| Tuberculous mastitis (immunocompromised, foreign born or travel to endemic area) |
| Bacterial abscess |
| Periductal mastitis |
| Trauma |
| Breast cancer |
| Other granulomatous inflammation of the breast (Table 1) |

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## Imaging

Imaging findings are non-specific and can mimic malignancy or acute infection (Benson and Dumitru, 2016). Mammography and breast ultrasound are the first step in work up. Mammographic findings of granulomatous mastitis range from an ill-defined density, possibly with spiculated margins to asymmetric density without margins. One series (Barreto et al, 2018) found that Breast Imaging Reporting and Data System category 4 (suspicious mammographic findings requiring biopsy) was most commonly given by specialised breast radiologists (American College of Radiology, 2013). Thickening of the overlying skin may also be seen and, in some patients, there may be no mammographic findings because of their increased breast density (Barreto et al, 2018; Valente and Grobmyer, 2018). In some cases, mammography may not be appropriate in the acute setting as a result of patient discomfort from breast compression.

On breast ultrasound an irregular hypoechoic lesion is seen, possibly with abscess formation with tubular extensions representing inflamed ducts (Johnson et al, 2016; Freeman et al, 2017). Lymph nodes may be enlarged with mild concentric cortical thickening and preservation of fatty hilum (Valente and Grobmyer, 2018). Use of magnetic resonance imaging in granulomatous mastitis has been suggested (Yilmaz et al, 2016); however, while it may be used to assess disease extent, it is rarely helpful as it cannot differentiate between inflammatory and malignant aetiology (Barreto et al, 2018).

## Histopathology

Histopathology is the cornerstone of diagnosis (Freeman et al, 2017; Barreto et al, 2018; Valente and Grobmyer, 2018). Core biopsy of the wall of the lesion is preferable to fine needle aspiration or excision biopsy, providing adequate information while being minimally invasive (Oran et al, 2013; Valente and Grobmyer, 2018). Histological diagnostic features are non-caseating granulomatous inflammation of lobular unit, multinuclear giant cells, polymorphonuclear leukocytes, plasma cells and possibly sterile micro-abscesses (Taylor et al, 2003; Barreto et al, 2018). Abscesses may be present in up to one-third of patients and, if present, aspiration should be attempted (Freeman et al, 2017; Valente and Grobmyer, 2018). In granulomatous mastitis abscesses, the central area tends to be thick necrotic tissue which is not amenable to aspiration. Any fluid collected should be sent for Gram stain and culture to evaluate the presence of bacterial and fungal microorganisms. Acid-fast bacilli stain to assess for *Mycobacterium tuberculosis* and appropriate assessment for *Corynebacterium* should be performed (Taylor et al, 2003; Johnson et al, 2016; Barreto et al, 2018; Valente and Grobmyer, 2018).

## Treatment

There is no consensus on the best treatment of granulomatous mastitis. Primary treatment should be based on disease severity and the patient's overall health (Benson and Dumitru, 2016; Valente and Grobmyer, 2018). Studies on treatment outcomes are mainly retrospective, contributing to poor understanding of the condition (Oran et al, 2013; Joseph et al, 2014; Freeman et al, 2017; Barreto et al, 2018). Treatment varies between countries, with socioeconomic factors contributing to these differences (Martinez-Ramos et al, 2019). Relapse following treatment is high, occuring in up to 20–50% of cases. However, studies have found that regardless of treatment type, the condition tends to be self-limiting over a period of 2–24 months (Benson and Dumitru, 2016).

### Initial treatment

As patients often present similarly to an acute bacterial abscess, percutaneous aspiration, oral antibiotics and regular clinical review are commonly undertaken. Antibiotics should be broad spectrum with anaerobic cover and non-steroidal anti-inflammatory drugs are recommended as best analgesia for inflammatory pain (Kiyak et al, 2014).

### Antibiotics

Once the diagnosis of idiopathic granulomatous mastitis has been established, long courses of antibiotics should be avoided (Valente and Grobmyer, 2018). For cases with identified *Corynebacterium*, appropriate antibiotics should be used with consideration of the lipophilic

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environment in which these bacteria are located. For this reason, β-lactams and fluoroquinolones with their low lipid solubility will be less effective. Antibiotics such as doxycycline or trimethoprim-sulfamethoxazole are lipophilic and more suitable. Care should involve infectious disease or microbiology specialist input as a prolonged course of antibiotics is likely to be required (Taylor et al, 2003; Dobinson et al, 2015; Johnstone et al, 2017).

## Expectant approach or watchful waiting

As most cases of idiopathic granulomatous mastitis are self-limiting, a trial of watchful waiting following an initial course of antibiotics is reasonable for mild localised symptoms. Regular clinical review should be carried out to ensure no disease progression as well as for patient reassurance. No deaths have been reported in the literature from septic complications in granulomatous mastitis (Valente and Grobmyer, 2018).

## Steroids

The mainstay of treatment for granulomatous mastitis of idiopathic nature is with steroids (Freeman et al, 2017; Valente and Grobmyer, 2018). There is no standard dose and various regimens are described in the literature, ranging from 10–60 mg prednisolone per day with dose reduction over many weeks (Oran et al, 2013; Aghajanzadeh et al, 2015). Alternatively, 0.5–1 mg/kg for 3 weeks with a tapering dose may be prescribed (Joseph et al, 2014; Skandarajah and Marley, 2015). Successful treatment with steroids was reported in up to 80% of cases, but up to 50% of these will recur, usually within 1–2 months after ceasing treatment. For these cases, a second course of steroids can be prescribed.

The decision to involve a rheumatologist will depend on the expertise of the treating breast clinician; the senior author recommends involving a physician if a steroid regimen is prolonged or a second course is required. Lower dose steroid regimens have been described by some authors (Freeman et al, 2017) and have the benefit of avoiding adverse side effects of cushingoid features, weight gain and hyperglycaemia. The choice between high-dose vs low-dose steroid use should be based on patient comorbidities. In successfully treated cases, the use of steroids results in complete resolution of inflammatory change including sinus tracts.

### Topical steroids

The use of topical steroids has been emerging as an effective alternate treatment to systemic steroids (Gunduz et al, 2014; Altinoprak et al, 2015; Çetin et al, 2019). A prospective randomised study (Çetin et al, 2019) compared topical steroids, systemic steroids and a combination of both. In the topical steroid arm, 42 patients were treated with 0.125% prednisolone cream for 5 consecutive days a week. Treatment was continued until clinical resolution of symptoms and ranged from 2–10 months. Complete clinical response was seen in 82.9%, 14.7% of these recurred. There was no statistically significant difference in outcomes in the systemic steroid and dual therapy groups. Another prospective case series (Gunduz et al, 2014) of 11 patients treated with topical steroids as monotherapy for idiopathic granulomatous mastitis found nine cases responded to an initial 12-week course. Two cases required a second course of topical steroid application. Two further cases recurred 5 and 8 months later; these patients continued on topical prednisolone until they had resolution of symptoms. No side effects or steroid-related complications occurred. This novel treatment remains an area of investigation with positive preliminary outcomes.

## Immune modulators

Methotrexate has been used successfully to treat idiopathic granulomatous mastitis and may be useful as second-line therapy for patients unresponsive to, or those who have significant side effects from, glucocorticoid treatment (Freeman et al, 2017). The suggested dose of methotrexate is 15 mg/week, which is considered low dosage. Case series (Joseph et al, 2014; Aghajanzadeh et al, 2015) report complete resolution of symptoms in 72–100% of patients who completed second-line treatment with methotrexate and steroid combined therapy. Duration of therapy in one study (Aghajanzadeh et al, 2015) ranged from 2–4 months. Treatment with methotrexate should be initiated by a rheumatologist in conjunction with a breast specialist to regularly review clinical progress. Side effects of the drug include alopecia and deranged liver enzymes which may limit treatment (Joseph et al, 2014).

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## Key points

- Granulomatous mastitis is considered idiopathic and its pathogenesis is poorly understood.
- *Corynebacterium* has been identified as a pathogen in a subset of cases of granulomatous mastitis termed 'cystic neutrophilic granulomatous mastitis'.
- Histopathological diagnosis by core biopsy remains key in diagnosis.
- The disease is chronic and relapsing in nature and patients must be counselled on realistic expectations.
- Management involves watchful waiting in mild disease and immunosuppressants in more severe disease.

### Surgical treatment

Surgical treatments, including incision and drainage of abscess and complete excision of the affected area, have been described with varying results. However, relapse rates are high and repeated surgical interventions should be avoided as they lead to poor cosmetic outcomes. Surgical excision has been associated with poor wound healing and fistula formation. Some authors (Freeman et al, 2017) advocate surgery as a last resort and after failure of medical therapy or if steroid therapy is contraindicated, for example, in pregnancy. A 15–23% recurrence following surgery alone can be expected and is dependent on clear surgical margins (Kok and Telisinghe, 2010; Freeman et al, 2017). Mastectomy is a last line approach for intractable symptoms with failure of all other approach (Valente and Grobmyer, 2018). The senior author recommends avoiding any localised surgery because it can lead to expectant wound breakdown and unacceptable cosmesis, taking the view that mastectomy may be the only useful surgical intervention for the rare case of severe refractory disease where this may be the patient's only relief. This non-surgical approach is supported by others (Skandarajah and Marley, 2015).

## Conclusions

Granulomatous mastitis is a rare disease and remains poorly understood. A cause of granulomatous inflammation should be excluded, including cystic neutrophilic granulomatous mastitis caused by *Corynebacterium.* Clinical suspicion with demographic assessment can avoid delays in diagnosis and inappropriate treatment. Management is challenging and appropriate patient expectation should be set. Treatment includes broad spectrum antibiotics initially, followed by watchful waiting in mild disease or steroid use in severe disease. Methotrexate is an option but should generally be reserved for end of line treatment. Surgical intervention should be very carefully considered and only reserved for intractable cases, and mastectomy should be a last resort.

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**Conflicts of interest**

The authors declare that there are no conflicts of interest.

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