

Perspective

Granulomatous lobular mastitis

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Abstract

Granulomatous lobular mastitis is an unusual breast benign inflammatory disorder with unknown aetiology. It is generally emerged with the clinical symptoms of breast mass, abscess, inflammation and mammary duct fistula. The diagnosis is made by histopathology with a chronic non-necrotizing granulomatous inflammation in lobules of the breast tissue as the microscopic feature. Therapy of granulomatous lobular mastitis consists of surgical, medication treatment or combination of both, but now researches suggest that observational management is an acceptable treatment.

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Introduction

Granulomatous lobular mastitis (GLM) is an unusual breast benign inflammatory disorder first described by Kessler and Wolloch in 1972.¹ The aetiology of GLM is unknown, but growing evidences suggest that a various of factors, including

microbiology agents, hormonal effect, and immunologic disorder, played an important role in disease occurrence.² The age range of GLM has been reported from 11 to 83 years old; however it mostly emerges in third and fourth decades women and was more frequently reported in the Mediterranean region and the developing countries in Asia.² GLM closely resembles the duct ectasia/periductal mastitis complex (DE/PDM) and tuberculous mastitis in the clinical manifestations and imaging examination.^{3,4} In microscopic features, it is a chronic non-necrotizing granulomatous inflammation in lobules of the breast tissue.⁵ No standard treatment exists for GLM. The main approaches are surgical, medication treatment or a combination of both, but now some studies suggest that observational management is an acceptable treatment.⁶ In this review, we describe the aetiology, clinical presentation, pathologic findings and differential diagnosis, as well as recommendations for treatment.

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Aetiology

The aetiology of GLM is not known exactly. A various of factors, including microbiology agents, hormonal effect, and immunologic disorder have been suggested of playing an important role in disease aetiology.

Microbiology agents

Corynebacteria are Gram-positive bacteria and members of the skin flora. They have been found in some patients with GLM recently and been considered to go deeper into the breast tissue via the ductal system. Taylor et al isolated *Corynebacteria* from breast tissue in 62 patients, who were diagnosed with GLM histologically, and 54.8% patients were bacteria-positive. Paviour et al⁷ carried on a research of 24 patients, and observed *Corynebacteria* in 12 cases by histopathological evaluation and diagnosed 9 cases with idiopathic granulomatous mastitis (IGM). *Corynebacterium kroppenstedtii* was the most frequently detected species in the studies mentioned above. In other literature,^{8,9} case presentations on *Corynebacterium* species have been mentioned as well, and species including *Corynebacterium amycolatum* and *Corynebacterium tuberculo-stearicum* were identified. *Corynebacterium accolens* was also proposed as a possible cause of GLM in a 23-year-old female.¹⁰

Hormonal effect

GLM is usually detected in women with a history of breast-feeding or birth recently. Gestation, breast-feeding and hyperprolactinemia have also been put forward as a possible pathogenesis of GLM. Documents and case reports have confirmed the hypothesis aforementioned. According to a study by Bani-Hani¹¹ et al, in the overall cases, 16.7% had active gestation, 16.7% had an experience of birth and breast-feeding within 6 months, and only 8.3% did not have a history of pregnancy. In 1984, Rowe¹² indicated co-morbid prolactinoma in a GLM case. Cases of GLM with hyperprolactinemia have also been reported in the following decades.^{12–14} A relation between GLM and breastfeeding as well as the hyperprolactinemia has been discussed but has never been elaborated in depth. A possible cause of GLM is the hormonal imbalance with a shift of the ratio among gestagen and oestrogen.¹⁵ With a hypothesis of autoimmune reactions to extravasated secretions from lobules, it becomes manifest intraductally by retention of secretions followed by ductal ectasia. The rupture of the ducts results in a persisting stromal cells inflammation.^{16,17}

Immunologic disorder

The association between GLM and erythema nodosum and ankle arthritis have been commonly studied recently. It has been proved that treatment with corticosteroid and immunosuppressants is effective for some patients, which are supported that GLM is a kind of autoimmune disease. In the report by Zen et al,¹⁸ one patient of granulomatous mastitis was observed with a lymphohistiocytic infiltrate, fibrosis, epithelioid granulomas without necrosis and an infiltrate of IgG4+ plasma cells. A conclusion of the report is that the GLM and IgG4-related autoimmune syndrome are possible highly correlated. Ogura et al¹⁹ reported 2 similar cases, in which an infiltrate of IgG4+ plasma cells was also observed, and it was proposed that GLM may consist of two subtypes: non-IgG4-related mastitis and IgG4-related mastitis. Although the autoimmunity of GLM has been put forward, tests for rheumatoid factor (RF) and antinuclear antibody (ANA) are negative in general. Ozel et al²⁰ conducted a research on 8 cases. In the research, 6 cases were RF positive, and only 2 were positive for ANA and anti-double stranded DNA. In consequence, there exists an autoimmune component in the aetiology of GLM.

The other factors

The other factors when considered about the aetiology of GLM mainly consist of alpha-1-antitrypsin (AAT), oral contraceptives (OCS) and smoking in general. As a member of the serine-protease inhibitor family, AAT is basically synthesised by hepatic cells. The deficiency of AAT causes lung and liver pathologies primarily. In 2001, Schelfout et al²¹ reported one GLM case with an AAT deficiency. OCS could promote the breast secretion and is deemed to be a potential aetiological factor of GLM. The range of the correlation between GLM and OCS is reported as 0–42%.^{22,23} In addition to AAT and OCS, a recent progress in the considerable studies is that smoking is related to the GLM, while an explicit reason has not yet been determined. Asoglu et al²⁴ presented that in a research with 18 GLM cases, 14 had a smoking history. According to a study by Baslaim et al,²² none of their 20 cases was a smoker nevertheless.

Clinical presentation

The GLM mainly occurs in premenopausal females shortly after their last childbirth. It is generally emerged with the clinical symptoms of breast mass, abscess, inflammation and mammary duct fistula. In addition,

chronic mass is a very common presentation of the GLM. The mass is hard and oedematous fixed to the skin, accompanied with an axillary node enlargement and nipple retraction occasionally, which is radiological and clinical findings of mimic breast cancer. Aspiration cytology is characteristic, showing leucocytes, giant cells, epithelioid cells and macrophages. Some patients are diagnosed with the abscess as well, which is a kind of tender breast lump with painful and inflamed overlying skin. The chronic breast abscess can evolve into fistulae following as the disease progresses.

Pathologic findings

Granulomatous lobular mastitis is characterized by non-caseating granulomas concentrated in lobules. The histopathologic features of GLM are the inflammatory background and significantly lymphoplasmacytic cells. Microscopical results presented the existence of numerous Langhans' giant cells, neutrophil polymorphs and epithelioid histiocytes in the granulomas. Besides, microabscesses, necrosis, sinus tracts, duct ectasia were also observed frequently.²⁵ Gram stains and microbial cultures of these samples are often negative in GLM cases, in some degree due to the fastidious nature of the organisms.

Differential diagnosis

Granulomatous lobular mastitis closely resembles the duct ectasia/periductal mastitis complex (DE/PDM) and tuberculous mastitis in the clinical manifestations and imaging examination.

The clinical manifestation of tuberculous mastitis resembles GLM, such as breast lumps, abscess formation and draining sinuses. Most of tuberculous mastitis patients do not have systemic symptoms, such as fever and weight loss,²⁶ and the aspiration cytology, tuberculin test and pathology examination of tuberculous mastitis can be even negative results, and sometime the Polymerase Chain Reaction molecular detection techniques is required in the meanwhile.²⁷ However, compared with GLM, patients with tuberculous mastitis are younger and have wider lesion range,²⁸ and the main pathological characteristics are caseation necrosis, with the incidence of caseation necrosis in tuberculous mastitis is over 90%, whereas in GLM it is 10%.²⁹

The DE/PDM is another nonpuerperal mastitis, which principally affect the major breast ducts. The pathogenesis of DE/PDM have yet to be elucidated, but in some studies, it is shown to be concerned with stimulation of squamous epithelium cornification,

infections and smoking.^{25,30} The DE/PDM closely resembles granulomatous lobular mastitis in the clinical manifestations and imaging examination, but when compared with GLM, more patients with DE/PDM are with nipple discharge and nipple retraction, and the breast masses are often beneath the areola.^{4,25,30} The typical pathological characteristics are duct ectatic which is closest to the nipple, while foam cells and decidual ductal epithelial cells exist commonly. Diffuse plasma cells infiltration, sometime even foreign body granuloma can be discovered around the ducts and lobules.⁴

Granulomatous lobular mastitis is also needed to be differentiated from sarcoidosis of the breast, foreign body granuloma, hidradenitis suppurativa and so on, in which systemic symptoms are apparent.

Treatment

No standard treatment exists for GLM. Observational management, surgical intervention and medication treatment (mainly to corticosteroids and immunosuppressive) are the general therapy method.

Observational management

Literature reports that GLM can be self-limiting with 6–12 months natural course to stable no matter what treatment had been taken, and more than half of GLM patients who do not receive any treatment revealed complete remission.^{6,31} Therefore the observational management is acceptable.

Surgical intervention

Surgical intervention is commonly used in present clinical practice, but it should be used with caution for 16%–50% recurrence rate was reported after surgical treatment,²⁷ and this can be related to the scope of surgical resection. To decrease recurrence rate, the negative surgical margins of inflammatory tissue must be achieved. While surgical intervention may also cause complications such as poor wound healing, chronic sinus formation and shape change of breast. For severe and intractable cases, mastectomy followed by breast reconstruction can be applied as a therapeutic option after discreet consideration.

Corticosteroids and immunosuppressive agents

Corticosteroids have been used as an conservative management, which have been reported can decrease the mass dimension as primary treatment and also could

be used in unresectable lesions before surgery. For resistant and complicated cases, corticosteroids should be administered after excision to prevent GLM recurrence.^{32,33} No standard therapeutic dose and course time of corticosteroids agents, and a daily dose of 0.5–1 mg/kg of prednisone is reported be effective treatment for GLM,³² however some studies suggest that high doses of corticosteroids should be continued until complete resolution.³⁴ However, infectious aetiology and other contraindications of corticosteroids should be excluded before agents are administered. Immunosuppressive agents such as methotrexate can be used as steroid sparing agents for patients with contraindication of corticosteroids or in relapse cases after corticosteroid discontinuation,^{23,35} and reports have suggest that low-dose corticosteroids together with methotrexate could be a reasonable option to decrease the side effects of corticosteroids.

Conclusion

GLM is a rare inflammatory disorder of the breast, and the pathogenesis of GLM had yet to be elucidated. GLM is needed to be differentiated from the duct ectasia/periductal mastitis complex and tuberculous mastitis. The histologic examination was the key method in diagnosis of GLM. No standard treatment exists for GLM. Observational management, surgical intervention and medication treatment are the general therapy method. Well-designed studies will be required in the future.

Conflicts of interest

All the authors had no potential conflicts of interest, including financial interests and relationships and affiliations relevant to the subject of their manuscript.

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