Review Article

Identification of periductal mastitis and granulomatous lobular mastitis: a literature review

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Background and Objective: Non-puerperal mastitis (NPM) is a breast disease with poor clinical manifestations, which seriously affects women's health and quality of life. Due to the low incidence rate of the disease and the paucity of related research, there is much misdiagnosis and mis-management of periductal mastitis (PDM) and granulomatous lobular mastitis (GLM). Therefore, understanding the differences between PDM and GLM, in terms of etiology and clinical manifestations, is crucial for patient treatment and prognosis. At the same time, choosing different treatment methods may not achieve the best treatment effect, so the appropriate treatment method can often reduce the patient's pain and reduce the recurrence of the patient's disease.

Methods: The PubMed database was searched for articles published from 1 January 1990 to 16 June 2022 using the following search terms: "non-puerperal mastitis", "periductal mastitis", "granulomatous lobular mastitis", "mammary duct ectasia", "idiopathic granulomatous mastitis", "plasma cell mastitis", and "identification". The key findings of the related literatures were analyzed and summarized.

Key Content and Findings: We systematically described the key points in the differential diagnosis, treatment, and prognosis of PDM and GLM. The use of different animal models for research and novel drugs to treat the disease were also described in this paper.

Conclusions: The key points in the differentiation of the two diseases are clearly explained, and the respective treatment options and prognosis are summarized.

Keywords: Non-puerperal mastitis (NPM); periductal mastitis (PDM); granulomatous lobular mastitis (GLM); identification

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Introduction

Non-puerperal mastitis (NPM) is a chronic inflammatory disease of the breast that occurs in non-lactating women. It mainly includes periductal mastitis (PDM) and granulomatous lobular mastitis (GLM) (1). However, differential diagnosis of the two conditions is hampered by the very similar clinical manifestations. Because the etiology of these two diseases is different, there are also obvious differences in the treatment. If these two cannot be accurately differentiated, treatment of them can be delayed and a poor prognosis can result. While there is a paucity of studies differentiating the two diseases, we herein summarized the available data and systematically described the key points in the differential diagnosis, treatment, and prognosis of PDM and GLM. In addition, different animal

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Table 1 A summary of the search strategy

Items	Specification
Date of search	16/6/2022
Database	PubMed
Search terms used	Non-puerperal mastitis; periductal mastitis; granulomatous lobular mastitis; mammary duct ectasia; plasma cell mastitis; idiopathic granulomatous mastitis
Time frame	1/1/1990 to 16/6/2022
Inclusion and exclusion criteria	All relevant articles in English language
Selection process	Selection was conducted independently and discussed routinely for consensus

Table 2 The different names for periductal mastitis

Disease	Name	Reference
PDM	Plasma cell mastitis	(2)
	Mammary duct ectasia	(3-6)
	Comedomastitis	(3-6)
	Mastitis obliterans	(3-6)
	Morbid condition of lactiferous ducts	(7)
	Mammary duct fistula	(8)
	Zuska disease, etc.	(8)

PDM, periductal mastitis.

models of these diseases for research were also described in this paper. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6473/rc).

Methods

The PubMed database was searched for articles published from 1 January 1990 to 16 June 2022 using the following search terms: "non-puerperal mastitis", "periductal mastitis", "granulomatous lobular mastitis", "mammary duct ectasia", "idiopathic granulomatous mastitis", and "plasma cell mastitis" (*Table 1*). The results from the identified literatures were analyzed and summarized.

Definition

PDM is a benign breast disease that mainly affects the breast ducts. It is characterized by dilatation of the diseased ducts and a large number of plasma cell infiltration around the ducts, and hence it is referred to as "plasma cell mastitis" (2). Terms including "mammary duct ectasia" (MDE), "comedomastitis", and "mastitis obliterans" have also been used to describe the disease (3-6). However, at present, researchers have different opinions as to whether MDE and PDM belong to different stages of the same disease or whether they are two different entities (6).

The disease was first discovered by Birkitt (7) in 1850 and was called "morbid condition of lactiferous ducts" because it can reach the dilated ducts under the areola with inflammation around the ducts. In 1951, Zuska *et al.* (8) described the nature of the disease as "mammary duct fistula", and it became known as "Zuska disease" (the various terms for "PDM" are shown in *Table 2*). A previous study has shown that duct ectasia accounts for 5–25% of all symptomatic breast diseases (9). The condition usually occurs in women under the age of 30 or during peri-menopause, but some cases have been reported in childhood and in males (10,11).

GLM is a granulomatous inflammation centered on the lobules (12,13). It was first reported by Kessler and Wolloch (12) in 1972. In 1987, Going (14) formally put forward the word GLM according to its morphological characteristics. In the process of clinical and scientific research, names such as "idiopathic granulomatous mastitis" (IGM) (15), "idiopathic granulomatous lobular mastitis" (IGLM) (16), and "cystic neutrophil granulomatous mastitis" (CNGM) (17) have been used to describe this condition (shown in *Table 3*), but the word "GLM" is still used most frequently in pathological diagnosis.

GLM is a rare non-lactation inflammatory breast condition that accounts for 24% of all inflammatory breast diseases (18) and comprises only 0.44–1.6% of breast biopsy samples based on pathologic and cytologic diagnostic criteria (19). However, in the literature, the terms GLM, IGM,

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Table 3 The different names for granulomatous lobular mastitis

Disease	Name	Reference
GLM	IGM	(15)
	IGLM	(16)
	CNGM	(17)

GLM, granulomatous lobular mastitis; IGM, idiopathic granulomatous mastitis; IGLM, idiopathic granulomatous lobular mastitis; CNGM, cystic neutrophil granulomatous mastitis.

IGLM, and CNGM are often used interchangeably (20), which results in inconsistencies regarding the statistical incidence of GLM. GLM usually occurs in women of childbearing age from 30 to 40 years old (21), and it is more common within a few years after delivery (22). Cases have also been reported in an 11-year-old (23) and an 83-year-old patient (24). The disease has been found around the world and in all races, but it is more common among Mediterranean, North African, and Asian countries (25,26).

Etiology

The etiology of PDM

Nipple invagination and mammary duct blockage

As early as 1958, Patey and Thackray (27) noted that the cause of PDM was mammary duct malformation and excretion disturbances (the etiologies of "PDM" and "GLM" are shown in *Figure 1*). The squamous epithelium at the opening of the duct extends to the dilated inner wall of the mammary duct, and its keratinized debris and lipid secretion blocks the lumen, resulting in inflammation of the duct walls (28). Nipple invagination is an important cause of mammary duct blockage, and the relationship between nipple invagination and PDM has been well documented (29,30). Nipple invagination is a common disease, with an incidence of about 3.26% in the whole population and 36.8% in patients with PDM (31,32). It is mainly caused by the pull of the fiber bundles or shortened breast ducts behind the nipple. Nipple invagination leads to poor drainage of the mammary duct and accumulation of a large number of substances in the mammary duct, leading to dilatation of the mammary duct, destruction of the elastic layer of the mammary duct, and overflow of catheter contents through the damaged catheter wall, resulting in long-term non-healing inflammatory reactions around the areola, which Ingier referred to as "mastiffobliterans" (33,34).

Smoke

The toxic substances from smoking can not only directly damage the subareolar duct, but also indirectly affect the release of hormones or blood flow, resulting in the growth of anaerobes, disturbance of mammary duct excretion, ductal dilatation, and inflammation (35). The pathological manifestation of this disease is squamous metaplasia of ductal epithelium, which may be caused by congenital factors, but it is more likely to be due to the effect of smoking on epithelial cells (36). The exfoliated epithelial cells can form a plug in the main duct behind the areola, thus blocking the proximal mammary duct. Obstruction caused by fragments and aggravation of ductal epithelial squamous metaplasia are good substrates for bacterial growth (34). PDM often occurs in heavy smokers (37) and the possibility of cultivating anaerobic bacteria in breast abscesses and the possibility of fistula in these people are increased. Relevant studies have confirmed that smoking is a major pathogenic factor of the disease (38-40).

Prolactin

Hyperprolactinemia can elevate lipids and proteins in breast secretions and increase the number of ductal epithelial cells, ductal histiocytes, and macrophages, suggesting that hyperprolactinemia may promote inflammation around and within ducts (41).

Obesity

Obesity is reported to be a risk factor for PDM. The higher the body mass index, the higher the incidence of PDM. Obesity may directly disrupt the local immune function of the breast and aggravate the development of PDM (2). It has been reported that obesity is associated with mild chronic inflammation, which destroys the immune function (2). In addition, obesity directly affects estrogen production and inflammation in the local breast (42). Although obesity is considered to be an important risk factor for PDM, this conclusion is only based on case reports and further research is needed to verify these results.

Reproductive factors

A previous study has shown that reproductive factors are related to PDM. Late menarche is an important risk factor for PDM, while increased age at parturition is a protective factor (2).

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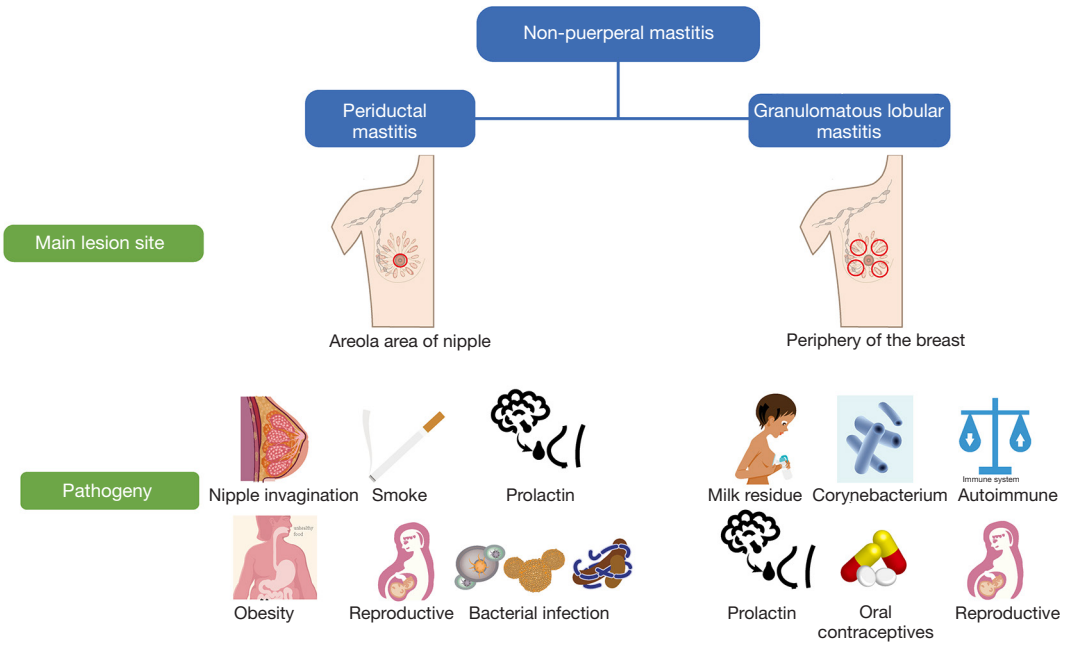

Figure 1 The different etiology of periductal mastitis and granulomatous lobular mastitis.

Bacterial infection

Bacterial infection is considered to be an important cause of PDM. Al Benwan *et al.* (43) believed that PDM was caused by bacterial infection, in which *Staphylococcus aureus* was the main pathogen of PDM, followed by Bacteroides and anaerobic *Streptococci*. Liu *et al.* (2) further confirmed the correlation between bacterial infection and PDM using 16SrRNA sequencing. The latter report found that the expression of interferon-γ and interleukin (IL)-12A was upregulated in breast interstitial inflammatory cells in patients with PDM. Interferon-γ and IL-12A are characteristic cytokines of T helper 1 (Th1) cells, indicating that Th1 cells play a role in the immune response of this disease. Th1 cells are very important for eradicating invasive pathogens, including bacteria, parasites, yeasts, and viruses, and it also suggests that PDM may be an inflammatory disease related to infection.

Etiology of GLM

At present, the etiology and pathogenesis of GLM are not clear. According to the related literature (17,23,44-51), alpha-1 antitrypsin deficiency, smoking, *Corynebacterium* infection, pregnancy, lactation, breast trauma, hyperprolactinemia, oral contraceptive, and autoimmune abnormalities may be involved in the occurrence and development of GLM.

Galactostasis

Brown *et al.* (52) believed that GLM may be caused by immune reactions and local hypersensitivity caused by residual milk after lactation. The pathological changes of GLM center around the breast lobule, and its mechanism may be increased milk secretion followed by siltation to destroy the structure of breast lobules and ducts. Secretion overflow into the stroma can induce local immune reactions and lead to granuloma formation (53). A previous study (54) showed that there was a higher rate of breastfeeding in patients with GLM and that breastfeeding mothers took longer to relieve symptoms than those who did not breastfeed. Therefore, it is speculated that the local residue of milk may be an important factor leading to GLM.

Corynebacterium

Corynebacterium infection may be closely related to the pathogenesis of GLM, especially *C. kroppenstedtii*, which has been detected in tissue samples of granulomatous mastitis and is believed to be the main cause of the disease (48,55-57). In 1998, Collins *et al.* (58) first isolated *C. kroppenstedtii* from sputum samples of Swedish patients. It is a gram-positive, aerobic, immobile, non-spore-forming, unstained rod-shaped bacteria, and is occasionally described in human infections, especially in granulomatous mastitis (59,60). In 2002, Paviour *et al.* (61) isolated *Corynebacterium* from

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diseased tissues, pus, or cotton swabs from deep wound tissues of 24 patients with mastitis. The most common strain was *C. kroppenstedtii*, followed by *Mycoplasma* and *Mycobacterium tuberculosis*. Yu *et al.* (62), through metagenomics and bioinformatics analysis, demonstrated that *Corynebacterium* accounted for 1.1–58.9% of the microflora of breast abscess in GLM patients. Further sanger sequencing and real-time fluorescence quantitative polymerase chain reaction (PCR) confirmed the growth of *C. kroppenstedtii* in 57.89% of the samples.

C. kroppenstedtii is a fussy lipophilic bacteria, which lacks the specific cell membrane fungal acid of other *Corynebacterium*, and its growth depends on the synthetic medium with appropriate lipids (58,59). The positive rate of Gram staining in paraffin tissue is relatively low (63). Even in positive cases, it is very difficult to determine the type of bacteria through microscopic observation because of the small number and small size of the bacteria. In addition, the culture conditions of the bacteria are harsh, the growth is slow, and it takes at least 72 hours to incubate, resulting in a low success rate of pathogen culture (48,64). Therefore, *Corynebacterium* cannot be cultured in conventional cultures, which lasts only 48 hours. The use of antibiotics before sampling (48) may also lead to negative culture results. For example, in the study of Johnstone *et al.* (65), although Gram staining and culture were negative, 16SrRNA gene sequencing confirmed the existence of *Corynebacterium*. To date, a large number of studies on pathogen infections have been reported, with most being based on the results of tissue culture, 16SrRNA, or other traditional detection methods, and all show that *Corynebacterium* may be the main pathogen (48,61).

Autoimmunity

Adams *et al.* (66) found that patients with GLM are often accompanied by erythema of both lower extremities, and that this suggests that the pathogenesis of the disease is related to autoimmunity. It has also been reported in the literature that granulomatous mastitis is accompanied by nodular erythema and arthritis (67). In addition, the breast may be affected by a range of autoimmune diseases that lead to chronic mastitis, including the following: (I) granulomatous diseases, such as sarcoidosis, Granulomatosis with Polyangiitis (GPA), or Crohn's disease; (II) connective tissue diseases, such as lupus or Sjogren's syndrome; (III) organ-specific autoimmune diseases, such as diabetes or thyroiditis; and (IV) systemic diseases, such as IgG4-related diseases or systemic vasculitis (68), suggesting that GLM may be an autoimmune disease.

Prolactin

Nikolaev *et al.* (69) found that hyperprolactinemia caused by intracranial tumors may have a direct causal relationship with GLM. Bouton *et al.* (70) suggested that prolactin may be a pathological factor involved in the occurrence of the disease. In addition, prolactin is considered to be a potential participant in autoimmune diseases such as lupus (71,72). Breastfeeding with high levels of prolactin appears to be a high-risk factor for rheumatoid arthritis or lupus attacks (73,74). A study has also demonstrated in lupus patients, that the immunosuppressive effect of regulatory T (Treg) cells on effector T (Teff) cells is significantly regulated by prolactin secretion (75). The potential immune effects of estrogen and/or prolactin on breast cells or breast underlying immune system may lead to an imbalance towards the pro-inflammatory axis and stimulate the occurrence of autoimmune mastitis.

In addition, many antipsychotic drugs can increase the secretion of prolactin due to their inhibitory effect on dopamine. Hyperprolactinemia caused by psychotropic drugs has been reported to be associated with idiopathic granulomatous mastitis (76,77).

Oral contraceptives and reproductive factors

GLM is most common in women of childbearing age, especially those with a long history of oral contraceptives (51). Women of childbearing age with a history of childbirth and lactation are mainly affected, while women who have not given birth, postmenopausal women, and men are rarely affected (78). Therefore, some researchers believe that oral contraceptives, production, or lactation may be potential causes of GLM (79).

Clinical manifestations

Clinical manifestations of PDM

The main clinical manifestations of PDM include aperiodic breast pain, nipple discharge, nipple invagination, subareolar mass with or without periareolar inflammation, and periareolar abscess or papillary fistula. The clinical manifestation is changeable. The acute stage is similar to acute suppurative mastitis, with more red, swollen, and hot pain; the formation of abscesses; and a more severe whole-body reaction. In the subacute stage, the systemic reaction is not obvious, but there are still lumps and dark red skin

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Table 4 The severity classification of granulomatous lobular mastitis

Degree of severity	Size	Symptom
Mild	<2 cm	Occasional mild pain
Moderate	2–5 cm	Collection needing aspiration drainage, one fistula and a small amount of discharge
Severe	>5 cm	Severe pain and multiple fistulas and ulcers with discharge more than 20 cc daily

observed on the breast. In the chronic stage, a deep breast mass develops, especially in the areola area. The course of the disease is long, with repeated attacks, and some patients may experience tumor rupture after the formation of chronic sinus which is difficult to heal (2,32).

Clinical manifestations of GLM

GLM usually presents as unilateral, tenderness and erythematous soft breast masses. Nipple discharge and skin changes can occur, including ulcers and sinus formation, and may be accompanied by enlarged axillary lymph nodes, especially in chronic cases (19,80-84). It usually involves one breast and can occur in every quadrant, except the area below the areola (85-88). The pathogenesis of GLM is unrelated to the shape of the nipple. However, the areola can be involved from the periphery after onset, resulting in nipple invagination (84,89). Patients with chronic GLM can develop fistula, aseptic abscess, and sometimes orange peel-like degeneration, similar to malignant tumors (25). Approximately 34% of GLM patients have extramammary manifestations (26), which typically includes systemic joint swelling and pain, and nodular erythema of the lower extremities (51,84).

Kaviani *et al.* (90) classified the severity of the disease according to the clinical manifestations as follows (*Table 4*): mild disease being breast mass <2 cm on ultrasonography, no ulcer or fistula, and occasional mild pain; moderate disease being breast mass 2–5 cm, collection requiring aspiration drainage, one fistula, and a small amount of discharge; and severe disease being breast mass >5 cm, severe pain and multiple fistulas, and ulcers with discharge more than 20 cc daily.

The condition of GLM is often phased and intermittent, with a certain remission period.

Diagnosis

Breast ultrasonography, mammography, breast magnetic resonance imaging (MRI), pathological examination, blood biochemistry, and bacterial culture are often used in the examination of PDM and GLM.

B-ultrasound of the breast

PDM and GLM lesions show irregular shape. Some PDM lesions may show typical ductal dilatation, the diameter of the ductal can be larger than that of 3 mm, and the echo or hypoecho of mobile secretions can be detected internally (91), which can be used to distinguish from malignant tumors. GLM usually presents as hypoechoic, irregular masses with tubular processes, multiple masses, parenchyma edema, sinus to the skin, ductal dilatation, and axillary lymph node lesions (19,92-95).

Mammography

Since the breast tissue of patients of childbearing age is often dense, mammography is usually non-specific, showing solitary masses or focal asymmetry, skin thickening or axillary lymphadenopathy (19,91-93,95-97). Tuli *et al.* (89) noted that the clinical symptoms of chronic mastitis and breast cancer are similar, and thus difficult to distinguish using imaging methods, leading to ease of misdiagnosis.

Breast MRI

The sensitivity of MRI in detecting NPM lesions is much higher than that of X-ray and ultrasound, which can show more deterministic features and significantly improve the detection rate of lesions and the accuracy of qualitative diagnosis (95,98). Due to the rich blood circulation of inflammatory lesions, all NPM lesions are significantly enhanced after enhancement, which is significantly different from the glandular background. Therefore, all NPM lesions can be detected by MRI plain scan and enhanced scan, which can help to determine the severity of the disease (94). Patients with GLM usually show oval, lobulated, enhanced mass or no mass enhancement in breast MRI examination (19,92,99). In dynamic contrast-enhanced scan, NPM shows

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single or multiple regional non-mass-like enhancement, and the enhancement form is inhomogeneous. With abscess formation, single thick-walled ring enhancement or multiple cluster ring enhancement is typical in the lesion (100). Annular enhancement can also be seen in breast cancer, but the tumor wall of breast cancer is significantly thicker than that of breast inflammatory lesions. The interval of enhancement is more common in breast inflammatory lesions. Most breast cancers reach a peak within 2–3 minutes after injection imaging, and then decrease rapidly (fast in and out) and time-signal intensity curve (TIC) is mainly type III (99). When the morphology of the breast lesion is malignant, regardless of its hemodynamic performance, it should be considered as malignant first. When the morphology is benign and the hemodynamics is malignant, the malignant should be excluded by biopsy.

Histopathology

The histopathology of PDM is defined as chronic inflammation of the breast, accompanied by mammary duct dilatation, plasma cell infiltration, and abscess formation (101,102). The lesion of PDM starts from the large duct in the areola area, and the duct is highly dilated microscopically. It mainly involves neutrophil infiltration in the acute phase and a large number of plasma cells and lymphocytes in the subacute phase, and sometimes a large number of foam cells and multinucleated giant cells appear (13).

The histological features of GLM are necrotizing chronic granulomatous lobulitis and abscess formation (12,13). Characteristic histopathological features include lobular non-caseous granuloma with epithelioid histiocytes; multinucleated giant cells, mainly neutrophils, accompanied by a varying number of lymphocytes, plasma cells, and eosinophils; and no necrosis. Negative microbiological examination is beneficial to the diagnosis of GLM. Microabscess formation and fat necrosis are common. Non-caseous necrosis and neutrophil-dominated background are important clues for the diagnosis of GLM (13,25).

Taylor *et al.* (48) divided GLM into the following five types according to pathological specimens: type 1 is GLM; type 2 is IGM with mammary duct dilatation; type 3 is acute mammary duct dilatation with suppurative granuloma; type 4 is granulomatous inflammation; and type 5 is unclassified inflammation. The above classification has a certain guiding significance for clinical practice.

The definite diagnosis of GLM requires histopathological examination and exclusion of other causes. This includes tuberculosis, brucellosis, filariasis, actinomycosis, sarcoidosis, histoplasmosis, Wegener's granuloma, giant cell arteritis or breast cancer, foreign body reaction, ductal dilatation (plasma cell mastitis, subareolar granuloma and PDM), and fat necrosis (103,104).

Bacterial detection

Pus obtained from the pus cavity should be routinely stained with Gram, cultured, and acid tolerance performed to evaluate bacterial, mycobacterial, and fungal infections (80). Pus culture of PDM usually shows multi-bacterial infection, but there have also been reports of single microbial infection of P*seudomonas*, *Enterococcus faecalis*, *Corynebacterium*, *Bacillus firmus*, *Bacillus*, and *Staphylococcus aureus* (2). Anaerobic infections may be more common in smoking PDM patients (102). *Corynebacterium* is considered to be an important pathogen of GLM. The lipophilic characteristics of *Corynebacterium* make it very easy to grow and proliferate in fat-rich breasts. If they leave the tissue, the nutrition needed for growth and culture is complex, the culture time is long, and the pus needs to be cultured many times in order to improve the detection rate (56,76). Gene sequencing has become a useful method for bacterial identification in recent years. Because of the evolutionary conservation of 16SrRNA in all bacteria, 16SrRNA gene sequence is recognized as the gold standard for bacterial identification, phylogeny, and classification, and has been widely used to identify *Corynebacterium* in GLM (105).

Test of proinflammatory cytokines

Study (2) has shown that proinflammatory cytokines such as interferon (IFN)-γ and IL-12A, may play an important role in the progression of PDM disease. Huang *et al.* (106) showed that IL-6 may play a crucial role in the immunopathology of IGM, and serum IL-6 and C-reactive protein (CRP) levels can be used as biomarkers for the evaluation of disease severity in GLM. Saydam *et al.* (107) demonstrated that the levels of IL-22 and IL-23 in patients with GLM were significantly higher than those in healthy people, suggesting that IL-22/23 may be potential markers for the detection of GLM disease. In addition, Çetinkaya *et al.* (108) revealed that a high neutrophil-to-lymphocyte ratio (NLR) was predictive of poor outcome in patients with GLM.

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Table 5 The different treatment options for periductal mastitis and granulomatous lobular mastitis

Disease	Treatment
PDM	Abscess puncture and drainage
	Surgery
	Mammary duct irrigation
GLM	Expectant management
	Antibiotics
	Surgery
	Corticosteroids
	Corticosteroids combined surgery
	Others

PDM, periductal mastitis; GLM, granulomatous lobular mastitis.

Treatment and prognosis

Treatment and prognosis of PDM

Abscess puncture and drainage

For PDM patients with abscess formation, subareolar abscess aspiration or puncture drainage can be performed at the same time of antibiotic treatment. In patients with recurrence less than 2 times and no fistula formation, the cure rate of this therapy is higher (109) (different treatment options for "PDM" and "GLM" are shown in *Table 5*).

Surgery

PDM is mainly treated by surgery, but the postoperative recurrence rate can be as high as 43% (28). A study (102) showed that if patients continue to smoke, the risk of recurrence is higher. In the acute stage of the lesion, broad-spectrum antibiotics combined with metronidazole should be used to control the inflammatory reaction, and the operation should be carried out when there is no obvious acute inflammation and the mass is stable and limited. The principle of the operation is that the focus must be removed completely and fully, with particular attention to thoroughly removing all the diseased tissues visible to the naked eye, and ensure the negative margin as far as possible, so as to minimize the chance of relapse (32). The timing and precautions of the operation include the following: (I) it is not easy to carry out surgical treatment in the acute stage, since the inflammatory reaction in the acute stage is serious, the tissue edema is obvious, and the boundary of the focus cannot be accurately identified, and thus it is easy to cause damage to the normal breast duct, or the shape of the breast may be affected by the excessive scope of the resection; (II) all lesions should be removed as far as possible, including the large mammary duct with dilated obstruction behind the nipple and areola; and (III) patients with sunken nipple should be operated on to correct the invagination of the nipple during the same operation (28,30,101).

Mammary duct irrigation

It has been demonstrated that mammary duct irrigation has a good therapeutic effect on PDM (101). It not only has a low failure rate and short healing time, but also is the least harmful method in invasive treatment. It will be a very promising treatment.

At this stage, the overall recurrence rate of PDM is still as high as 50%. A study has shown that the recurrence rate of PDM without breast duct resection is as high as 79%, and the recurrence rate after resection is reduced by 28% (110).

Treatment and prognosis of GLM

The treatment of GLM includes expectant management, antibiotics, steroid therapy, immunosuppressive drugs, and surgery (19). Martinez-Ramos *et al.* (26) systematically reviewed the clinical characteristics and treatment of 3,060 patients with GLM. It was found that corticosteroid therapy was the most common treatment, with 69% of the patients treated with corticosteroids and 65% undergoing surgical treatment.

Expectant management

GLM may be a self-limited process, with up to 50% of patients undergoing remission spontaneously over a period of 6–12 months (19). Therefore, for patients with mild disease and imaging lesions less than 1–2 cm, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia and expectant management is an alternative (19,111,112). In the report by Lai *et al.* (24), 50% of GLM cases remitted spontaneously without any treatment, with an average interval of 14.5 months for complete remission.

Antibiotics

There is no unified conclusion on whether antibiotics are beneficial to the treatment of GLM. Wilson *et al.* (113) believed that antibiotics do not play any role in the treatment of GLM. However, with the continuous progress of detection technology, increasingly, more studies (48,62) have demonstrated the relationship between bacterial

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infection and GLM. Some studies have examined the use of antibiotics for a period of 2 weeks of empirical treatment (114), with good results (115). Recently, a series of investigations (83) have shown that extended oral doxycycline treatment (average 4.6 months) had a good therapeutic effect even in the absence of a clear bacterial infection, although the mechanism of this effect remains unclear. Dobinson *et al.* (55) suggested that short-term antibiotic treatment (5–7 days) cannot improve the clinical symptoms of GLM patients, but patients are often given short-term antibiotic regimens in daily treatment.

In addition, *Corynebacterium* is considered to be an important pathogen of GLM (48,55-57). Early identification of *Corynebacterium* infection and early administration of antibiotics may help to improve the cure rate of patients. Commonly used specific antibiotic therapies include clarithromycin, methoxide-sulfamethoxazole, penicillin, doxycycline, erythromycin, clindamycin, rifampicin, and tetracycline (115). Lipophilic antibiotics are more likely to reach sufficient concentrations in lipomatous granulomas, and optional drugs include doxycycline and methoxide-sulfamethoxazole, as well as clarithromycin and rifampicin, which can also be used to treat other granulomatous infections, including *Mycobacterium non-tuberculosis* (18,55).

Surgery

According to the theory that GLM may be an autoimmune disease formed by the immune response of breast duct contents to breast ductal epithelial cells (52), surgical resection of the focus involves the removal of the target antigen, so the optimal method is to reduce the original focus through comprehensive drug therapy, and then perform open surgery or minimally invasive rotary resection of the remaining "core focus area".

Lei *et al.* (116), through meta-analysis of 602 patients, found that surgical resection of the focus is the most direct, effective, and rapid method to achieve complete remission, and surgical treatment can achieve high complete remission rates and low recurrence rates irrespective of whether corticosteroids is used or not. Extensive resection with negative incisal margin is better than limited resection alone, because the latter has a higher recurrence rate (103,117). Therefore, the accurate evaluation of the lesion size by MRI before an operation may serve as a safe and effective measure to determine the success of extended resection of lesions in the treatment of granulomatous mastitis (94). However, the conclusions of some studies (80,118) showed that despite the high success rate of surgical treatment, the risk of recurrence still exists, and the recurrence rate of surgical treatment is similar to that of non-surgical treatment. Moreover, because GLM usually presents as a fairly large breast mass, surgical resection often leads to poor plastic results and severe breast malformations. In order to improve this result, Zhang *et al.* (119) have conducted clinical study on stage I implant breast reconstruction after surgical resection of lesions. The results showed that after primary prosthesis implantation, patients had higher breast shape satisfaction (88.9%) and lower postoperative infection rate (5.6%), suggesting that this method can be used as an optional method for breast reconstruction in patients after larger lesion resection.

Corticosteroids

In clinical treatment, corticosteroids are widely used in the treatment of GLM (120). DeHertogh *et al.* (121) were the first to describe the use of steroids in the treatment of GLM, with good results. Subsequent researchers (122-124) also reported cases of successful treatment of GLM with glucocorticoids.

Oral steroids are commonly used in the treatment of GLM, and recent meta-analyses (111,116) showed that the complete remission rate of this therapy is 71.8%. High-dose steroids (60 mg/day for 2 weeks) can improve the remission rate of patients. A randomized clinical trial by Montazer *et al.* (125) found that compared with low dose, GLM patients with high dose of corticosteroid had higher remission rates and lower recurrence rates. In addition, a study by Bani-Hani *et al.* (23) demonstrated that steroid therapy can reduce the risk of breast malformation after surgical treatment. However, only when GLM is clearly diagnosed by standard pathological examination can there be indications for corticosteroid therapy.

However, long-term oral administration of corticosteroids can lead to drug side effects such as concentric obesity, digestive tract ulcers, and impaired glucose tolerance (114), and after stopping treatment, the recurrence rate of hormone therapy is about 17–50% (125).

The local use of steroids is a new and effective treatment. A recent small randomized controlled trial (126) revealed that the efficacy of intralesional steroid injection was similar to that of oral steroids. Intralesional steroid injection is a relatively new treatment, which is equivalent to oral hormone therapy and avoids the side effects of systemic steroid therapy (127). The existing treatment plan (127) suggests that triamcinolone acetonide of 40 mg/mL should be mixed with 1% lidocaine (2 mL) and diluted with

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normal saline for intralesional injection, and the dose of triamcinolone acetonide can be adjusted according to the severity of the disease and the number and size of skin lesions. For patients treated with this method, the time for symptom relief was about 2 months (128). Other researchers (80) have also shown that 0.125% prednisolone cream used as a local steroid treatment for 5 days a week, over a course of 2–10 months, achieved the desired results.

Corticosteroids combined surgery

Some reports (116,129) have recommended that sequential surgery with steroids should be used as a first-line treatment for patients with pathologically confirmed GLM. Compared with oral corticosteroids therapy or surgery alone, the recurrence rate of corticosteroids combined surgery can be reduced to 2–4%, with good cosmetic effect. For complex and drug-resistant cases, or patients who have only undergone open biopsies, steroids can be given after resection, and for initially unresectable lesions, steroid treatment before surgery can also improve the success rate of surgery (103). In addition, local injection of triamcinolone acetonide combined with surgery appears to be a promising treatment.

Others

Recent studies (130,131) have shown that methotrexate (MTX) is effective in the treatment of GLM. Experts agree that methotrexate, an immunosuppressant, should be used for non-corticosteroids sensitive GLM (19,132). Folic acid should be supplemented to prevent the occurrence of folic acid deficiency syndrome when treated with methotrexate. At the same time, regular reexamination is needed to prevent interstitial pneumonia and other complications, and surgery should be performed after the focus is stable or reduced. The use of methotrexate is limited by contraindications and treatment side effects, including myelosuppression, oral ulcers, and hepatorenal dysfunction (19,80). The recommended dose can be from 7.5 to 25 mg/week, but several studies have suggested that the initial dose is 15 mg/week. The remission rate can be as high as 81–93%, and the average course of treatment is 8–10 months (132,133).

Patients with hyperprolactinemia should be treated with bromocriptine. For GLM caused by antipsychotic drugs such as risperidone, antipsychotic drugs should first be adjusted, and then the disease can be obviously relieved or cured, and the focus can be removed, only if necessary.

Cancerization

Investigations (134,135) have shown that patients with non-lactation mastitis may have an increased risk of breast cancer. In addition, a recent study (136) conducted in a large Chinese population showed that patients with a history of non-lactation mastitis have a higher risk of breast cancer, especially those under the age of 50, with low socioeconomic status, or receiving hormone medication. However, at present, there is a paucity of data on the mechanism of carcinogenesis caused by the disease, and future research should focus on the mechanism, prevention, and treatment of the condition.

Animal model

Yu *et al.* (137) injected the lesion homogenate of patients with periductal inflammation with Freund's adjuvant into the mammary gland of mice. A week later, the inflammatory lesions and infiltration of lymphocytes and plasma cells were observed in the mammary gland of the mice. Liu *et al.* (138) injected a mixture of normal breast tissue homogenate of healthy patients with Freund's adjuvant into the mammary gland of mice, and further injected IL-6 into the mammary gland of mice 3 weeks later. Thereafter, a large number of lymphocytes and plasma cells were observed in the mammary glands of the mice, which was considered to have induced PDM in the mice. The authors believed that the pathological manifestations of these two animal models are similar to those of PDM. A large number of inflammatory cell infiltration could be observed in the inflammatory lesions, suggesting that this is a good animal model to support further scientific research. However, this is a short-term model and it is unclear whether it can simulate a chronic disease process similar to non-lactation mastitis. In addition, the animal model was only compared with the pathological manifestations of PDM, and did not show any similarity or difference with the pathological manifestations of GLM. Since both PDM and GLM pathologically show a large number of inflammatory cell infiltration, the accuracy of the definition of the disease model warrants further examination.

Prospects

Although non-lactation mastitis is a benign disease, its poor local performance often leads to breast redness and swelling, ulceration, and even deformity, which can

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severely affect the health and quality of life of patients. Furthermore, available treatments are not ideal and patients easily relapse. While there has been much progress in the field of breast cancer treatment, we are still in the infancy of understanding non-lactation mastitis. Therefore, more research should be conducted to investigate the etiology and treatment of the disease. For example, for the association of pathogenic infection with NPM, whether the bacterial infection precedes the onset of the diseases or the diseases cause a secondary bacterial infection? We believe that NPM is an autoimmune disease, but there is no clear correlation between inflammatory factors or autoantibodies with the disease, which also requires further research. Although Corticosteroid therapy, surgery, and other methods have shown success to a certain extent, for most patients, there is still a very high risk of recurrence, and the treatment cycle can be as long as several months to several years. Therefore, an in-depth understanding of the pathogenesis of the disease, as well as the identification of novel and effective treatment methods is crucial. With the development of gene sequencing technology, a variety of bacteria, including *Corynebacterium kroppenstedtii*, have been detected in the lesions of patients. This provides a novel direction for studying the etiology of the disease. In addition, the influence of bacteria on the human body and the interaction between the two have become the focus of a variety of clinical research, which can undoubtedly broaden our thinking and change our previous fundamental concepts of treating diseases. At the same time, a variety of tumor necrosis factor inhibitors, including etanercept and adalimumab, have been successfully used to treat GLM patients who are resistant to systemic steroid therapy (21,139). Goulabchand *et al.* (68) believed that granulomatous mastitis may be one of the manifestations of giant cell arteritis. The pathogenic role of malregulated IL-6 in rheumatoid arthritis, juvenile idiopathic arthritis, Castleman's disease, giant cell arteritis, and other diseases has been demonstrated by the effectiveness of targeted IL-6 therapy (140). Therefore, biological agents targeting IL-6 signal transduction may also reduce the local inflammatory response of GLM. In addition, tocilizumab, sirukumab, anakinra, ustekinumab, and secukinumab have been shown to be effective in the treatment of giant cell arteritis (141-146). In the future, these drugs could also be used as research subjects for the treatment of NPM. These new detection techniques and therapeutic drugs have increased our understanding and treatment of non-lactation mastitis.

Conclusions

Due to the very similar clinical manifestations of PDM and IGM, as well as their complex nominations and unclear pathogenesis, patients are often given incorrect clinical diagnoses and treatment regimens. We can accurately identify and treat these two diseases based on pathological examination and different sites of the disease. At the same time, different clinical symptoms and treatment options are accompanied by different clinical outcomes, so the selection of treatment plans warrants comprehensive consideration. Firstly, the most reliable way to accurately diagnose the disease is pathological biopsy, which makes the diagnosis according to the typical pathological results rather than just relying on clinical manifestations. For patients with PDM, complete excision of the lesion in the non-acute phase usually cures the disease and if an abscess is formed, abscess puncture and drainage can be performed, and Mammary duct irrigation may also be an option. For GLM patients, the underlying causes should be identified first. Bromocriptine should be used to lower elevated prolactin. Bacteriological tests, such as 16SrRNA sequencing, are performed to identify possible pathogens and antimicrobial therapy is tried. Lipophilic antibiotics should be chosen for patients who are positive for *C. kroppenstedtii* and the duration of treatment should be appropriately prolonged, which is very important for early diagnosis and the selection of the appropriate treatment. Secondly, according to the size of the patient's lesion, the severity of the patient's lesion is graded. Patients with mild symptoms at the first time of treatment can choose expectant management and those who have ineffective expectant therapy or severe symptoms can choose glucocorticoids or immunosuppressant therapy; surgical resection is chosen when conservative treatment is ineffective, but the timing and method of surgery should be accurately grasped. In addition, new detection techniques and treatment methods are gradually becoming the focus of future research.

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