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Progress in etiology and diagnosis of granulomatous mastitis

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Abstract: The non-lactation mastitis is a chronic inflammatory disease. In accordance with the causes can be divided into specific mastitis and non-specific mastitis. Non-specific mastitis is common in granulomatous mastitis and plasma cell mastitis. Due to the unclear etiology and pathological mechanism, the treatment effect is not ideal. And it is easy to delay recurrence, which makes the patient in a long-term dilemma. In recent years, the incidence of granulomatous mastitis increased year by year. Scholars at home and abroad have made in-depth studies on the etiology and pathological mechanism of granulomatous mastitis. There are mainly two views, autoimmune reaction mechan and the factors of bacterial infection. New risk factors are being identified. This article reviews the etiology and diagnosis of granulomatous mastitis.

1. Introduction

In recent years, the incidence of Granulomatous mastitis (GM) has been increasing, which may be related to the lack of attention paid to early diagnosis and low diagnosis rate of patients, as well as the lack of early diagnosis and differential diagnosis. GM Early differential diagnosis allows the clinician to effectively intervene early to prevent the disease from becoming severe enough to necessitate surgical resection.

2. Background

GM was first reported in 1972[1], the disease is a kind of benign mammary gland inflammation, GM histology of certainty diagnosis lies in the existence of the special distribution of granulomatous lobular, clinical manifestations are pain, lumps, congestion and inflammation, and other symptoms are areola shrinkage, fistula and ulcers, and as much as 50% of patients could be erythema and swelling, Up to 15% of patients are characterized by lymphadenopathy[2]. Breast lesions can occur in any quadrant, but most occur in the posterior region extending radially from it, and most lesions are

unilateral[3]. Most cases reported in the literature show that GM mainly occurs in young women of childbearing age who have a history of breastfeeding, usually about two years after breastfeeding[4], and a few occur in pregnancy[5], occasionally seen in men[6]. Patients with GM may have recurrent abscesses for weeks or months. These results are clinically similar to bacterial abscesses or breast cancer, making diagnosis difficult. Non-specific symptoms can be misleading during diagnosis, so the time between symptom onset and definitive diagnosis may last for several months.

3. The cause of

Currently, GM can be clinically divided into two forms: Specific Granulomatous mastitis (SGM) and Idiopathic granulomatous mastitis (IGM). SGM is a disease caused by chronic granulomatous infection such as Wegener granulomatosis, sarcoidosis or tuberculosis. When no underlying etiology or association is identified, it is called IGM, and the postoperative recurrence rate of IGM is high[7]. The etiology of IGM is not clear, so there is no consensus on treatment plan.

3.1 Immunology

Currently, IGM is considered to be an autoimmune response to milk proteins in breast interstitial tissue caused by microtrauma secondary to infection, trauma or chemical stimulation[8]. Isolated deoxyribonucleic acid (DNA) from pathological specimens of patients diagnosed with IGM, and conducted molecular analysis on many bacteria including Corynebacterium and the most common infectious factors, but no bacterial DNA was detected. No bacterial growth in culture samples collected prior to initiation of treatment (surgery or steroids)[9]; The effective rate of antibiotics for empirical treatment is low. In addition, T lymphocytes play a dominant role in the immunohistochemical examination of biopsy specimens[10]. IGM is sometimes associated with erythema nodosum, peripheral arthritis and other autoimmune diseases. In addition, compared with human leucocyte antigen (HLA) from healthy persons, HLA-A*10, HLA-A*2403, HLA-B*18 and HLA-DR*17 antigens appear at significantly higher frequency in IGM patients. The frequency of HLA-A*29, HLA-B*14, and HLA-DR*1 is low[11], which proves that immunomodulatory function plays A role in the control of the disease, and the etiology of IGM is unlikely to involve bacteriological factors. Surgical treatment is a common treatment for IGM. It can quickly remove the lesion, and the treatment period is short, but the risk of recurrence and recurrence is high. Moreover, surgical removal of benign breast lesions may increase the risk of malignant tumor. At the same time, the stress and fear of surgical treatment, scarring or breast asymmetry caused clinicians and patients to seek more conservative treatment. Tang[12] the study found that such as topical steroids may be a first-line therapy for the treatment of IGM options, but in the use of steroids before must be ruled out the cause of the infection, because steroids may enhance infection, and short-term applications of steroids may make IGM recurrence rate is higher, the application of long-term, high dose may cause serious side effects. Studies[13,14] found that methotrexate combined with steroids not only ensured long-term remission of symptoms but also effectively reduced recurrence rates. These findings suggest that conservative treatment can effectively treat IGM and reduce the need for surgical resection.

3.2 Bacteriology

In recent years, the rapid development of microbial detection technology has provided more and more evidence for the correlation between bacterial infection and IGM. The association between HUMAN GM and corynebacterium infection was first reported by Binelli[15] in 1996. Corynebacterium is part of the normal microbiome of skin, mucous membrane, and fluid (including breast milk), and it is difficult to distinguish infection, colonization, and contamination, so missed

diagnosis may occur in GM cases, but corynebacterium detection is dominant in abscess specimens [9]. In addition, in recent years, GM combined with Corynebacterium infection, especially recurrent cases, especially Kroppnstedtii corynebacterium was more common. Yu[16] found that C.kroppenstedtii was the main growth of corynebacterium through Sanger sequencing and real-time quantitative PCR detection. C. Kroppenstedtii is a finicky, slow-growing Gram-positive bacterium with a 72-hour incubation period. Given the nature of this growth, breast biopsies tend to show only small amounts of microbial growth, further increasing the likelihood of false negative reports of infection and therefore misdiagnosis as IGM. Saraiya[17] showed that C.kroppenstedtii lacks the fatty acid called Mycolic acid in its cell membrane, so it needs to grow in a lipid environment. And lipid-rich breast tissue provides a perfect habitat for them to live in and form granulomas or abscesses. 5% sheep or horse blood AGAR can improve its growth, and the hyperlipidemia plate of Twain 80 not only significantly improves the positive rate of corynebacterium culture, but also significantly improves the colony morphology, which can be quickly identified and accurately obtained clinically[18]. C. Corynebacterium croppenstedtii has a biochemical property that it can hydrolyze Esculin. A new selective medium is composed of 10% galactose, 10% tine, fosfomycin and Esculin. Fosfomycin can inhibit many clinically common bacteria. Esculin is helpful for the identification of C.kroppenstedtii lipophilic Corynebacterium. C.kroppenstedtii lipophilic corynebacterium usually presents as 1-2mm greyish white colonies with a black halo around the colonies when cultured on a new selective medium for 72 h (35℃, 5% CO2). And has a pungent vinegar smell[19]. Therefore, the main reason for clinically ineffective treatment of IGM may be that most antimicrobial agents are hydrophilic and have weak distribution in lipid environment[20]. In addition, in the study of Wang[21], the pathogens of IGM patients were mainly pseudomonas aeruginosa and other non-corynibacterium pathogens, and some related cases proved that GM was closely related to histoplasmosis and other fungal infections[22].

3.3 Other pathogenic factors

At present, in addition to the two factors of autoimmunity and bacterial infection, other pathogenic factors have been reported.

Hormone imbalance hypothesis is widely recognized at present, women are prone to endocrine disorders during pregnancy, abortion and breastfeeding. 89% of IGM patients in Yuan[23] had more than two children, which indicates that multiple pregnancies may cause changes in the patient's internal environment, thus leading to IGM. A third of the cases involved an abortion, a forced termination of pregnancy that can also abruptly alter a woman's hormone levels and immune status. Endocrine disruption therefore plays an important role in the development of IGM. There is increasing evidence that IGM is associated with hyperprolactinemia, which leads to persistent production of intraductal secretions in the breast, which is likely to cause a local immune response, and which can also be secondary to antipsychotic drugs (e.g. Risperidone) and pituitary adenoma, risperidone can affect the secretion of dopamine, promote the expression of prolactin gene, and ultimately lead to hyperprolactinemia, and the dopamine agonist bromoprotin has a good therapeutic effect[24,25]. Therefore, it is important to measure serum prolactin in the diagnosis of IGM. In addition, age at first birth, obesity and oral contraceptives can also affect the body's hormone levels and increase the risk of the disease.

Trauma: The results of most current studies show that breast trauma will affect the integrity of breast structure, thus increasing the risk of breast structure damage and rupture. Prolonged breastfeeding may lead to long-term dilation of milk vesicles and ducts[26], and during mastectomy, if the lesion is not completely removed, IGM may become more severe due to surgery-related trauma[23], so trauma may be one of the pathogenicity factors of IGM.

Sjogren's syndrome is an autoimmune disease affecting the exocrine glands, mainly leading to lacrimal and salivary gland infiltration[27]. The anatomy, histology, and physiology of the salivary gland and mammary gland are similar, both belong to related mucosal immune system effector sites, and their ductal cells share receptors. In existing cases, patients with sjogren's syndrome may develop breast symptoms (recurrent mastitis, nipple discharge, or breast mass) prior to the onset of systemic symptoms of sjogren's disease[28], so sjogren's syndrome may attack the breast during its pathogenesis and affect the occurrence and development of IGM.

In fact, the majority of cases in the US mainly occur in non-white patients, and the incidence is even lower in Europe (especially Germany)[3], while the incidence is gradually increasing in Asia. Bercot[29] proposed that Nod2 gene mutation can increase the risk of IGM. This situation suggests that IGM may be susceptible to genes, leading to ethnic differences, so family history is a factor that cannot be ignored.

4. Differential diagnosis

Early diagnosis allows us to detect the disease in time and initiate appropriate treatment strategies more quickly, thus improving the general prognosis of the disease.

4.1 IGM and tuberculosis

IGM clinical and radiographic findings were similar to those of breast cancer and tuberculous mastitis. At present, the gold standard for the diagnosis of GM is histopathological testing. When conducting biopsy, acid-fast staining, tuberculous and non-tuberculous genetic testing, and fungal culture should be performed simultaneously. Because there are multiple etiologies that can cause symptoms of breast granulomatous inflammation, IGM can only be considered if malignant tumor and infection are excluded in clinical diagnosis. Therefore, differential diagnosis of IGM is essentially a process of excluding other diseases. Tuberculosis is still prevalent in different regions of China, the breast is an uncommon part of tuberculosis, and it is difficult to identify tuberculosis bacilli in breast tissues. Therefore, IGM is suspected to be the result of undiagnosed tuberculosis, and more detailed examination of tuberculosis should be conducted along with the diagnosis of IGM[30-32].

4.2 IGM and other related mastitis

IGG4-related Diseases (IGG4-RD) is a group of chronic and recurrent inflammatory conditions, which may involve multiple sites (such as pancreas, periorbital tissues and thyroid gland). According to international consensus standards, the main diagnostic criteria for IGG4-RD include (a) lymphocytic infiltration; (b) Fibrosis, at least locally matted; (c) Phlebitis obliterans. Secondary criteria were (a) phlebitis without lumen occlusion, and (b) eosinophilia. Diagnosis of IGG4-RD requires at least two main criteria[33]. Recently, it has been reported that IGG4-RD may occur in the breast. Allen[34] showed that although IGG4-associated mastitis and IGM share many common characteristics, more of them are manifested as two independent breast diseases. The histological appearance of IGG4-RD depends on the specific organ involved. Based on the consensus statement of IGG4-RD in a large number of cases and the histological description of IGM in the literature, a classification model called Michigan was created. To be classified as the most likely IGG4-associated mastitis, a sample must meet at least four of the five positive criteria and two of the three negative criteria. The positive criteria were: intensive lymphoplasmic cell infiltration, fibrosis, obliterans phlebitis, & GT; 10 IgG4+ cells/HPF, & GT; 40% IgG4/IgG ratio; The negative criteria are epithelioid tissue cells, well-formed granulomas, and giant cells. IGM in giant cells or well-formed granulomas in the breast is very diagnostic.

Although the clinical manifestations and treatment of IGM and plasma cell mastitis (PCM) are roughly the same, most of the current evidence confirms that IGM and PCM are two different breast diseases. The incidence of inverted papilla in PCM is significantly higher than that in IGM, and erythema nodosum (EN) mainly occurs in IGM, which is more severe in EN patients because it presents more bilateral and diffuse breast symptoms[35]. Jiang[36] found in the retrospective analysis that IGM masses were usually larger than PCM masses and were more prone to suppuration or ulceration. Histopathologically, IGM showed a higher incidence of granuloma and microabscess formation in lobules and surrounding tissues and a higher number of multinucleated giant cells in granulomas compared with PCM. In PCM patients, intraepithelial or peristromal foam cells are more common than in IGM patients. These clinical manifestations enable clinicians to distinguish between the two diseases at an early stage and effectively intervene with empirical treatment.

4.3 Immunological indicators related to IGM

Some scholars have also discussed the changes of immune indexes and other related factors during the initial onset, development, outcome and prognosis of patients. Koksal[37] found higher levels of IL-8, IL-10 and IL-17 in peripheral blood of IGM patients, and IL-8 helps prove neutrophil chemotaxis, which plays an important role in inflammation. Il-10 is a powerful anti-inflammatory cytokine used to evaluate T and B regulatory cells. Il-17 stimulates the production of IL-6 and IL-8. Saydam[38] found elevated levels of serum IL-22 and IL-23 in IGM patients. Interleukin-23 is a member of the IL-2 cytokine family and can directly stimulate Th17 cells] to produce IL-17, which is usually related to the induction of allergic reactions, and il-22 regulates antibody production. By activating signal transducers and transcriptional activator 3 (STAT3) signal cascade, the antibacterial effect of JAK2-STAT3 pathway inhibitors provides a certain basis for the treatment of human IGM, il-17 and IL-22 together may induce the expression of antimicrobial peptides in keratinocytes[39]. Yigitbasi[40] found that IL-33 and soluble interleukin-33 ST2 receptor (IL-33-ST2 receptor) have high sensitivity and specificity in differentiating GM from breast cancer. Serum endotoxin is a new specific molecular biomarker, which is upregulated in cancer and rheumatoid arthritis and other chronic inflammatory diseases. Therefore, increased serum endotoxin level may be a marker of potential chronic inflammatory diseases[41].

5. Conclusions and Discussion

In conclusion, granulomatous mastitis may be a non-specific disease caused by a variety of factors, so the study of its pathogenic factors can control the disease and prevent the disease on the whole. The research on new selective media and specific markers is helpful to provide valuable diagnostic basis in the early stage of the disease and monitor the development process and prognosis of the disease. These are the focus of the research on the diseases that cannot be conquered in the medical neighborhood and the diseases of unknown etiology.

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