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Research Progress on Pathogenesis and Treatment of Non-lactation Mastitis with Traditional Chinese Medicine

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Abstract: ***Non-puerperal mastitis (NPM) is a chronic inflammatory disease which is mediated by many factors and tends to occur in non-lactating and non-pregnant women. Its long course of disease, protracted difficult to cure, easy to relapse, to the patient's economy and psychology caused a huge burden. Modern medicine has made many researches on the pathogenesis of NPM, but there are still some deficiencies. At present, the main treatment methods for NPM include anti-infection, hormone therapy, immunosuppressant, surgical resection of the lesion, etc., but many adverse reactions are prone to occur, so it is very important to seek more high-quality, safe and economical treatment means. With the development of traditional Chinese medicine in recent years and the deepening of the research on NPM, the advantages of traditional Chinese medicine in the treatment of such diseases have become increasingly prominent. By referring to relevant data and literature, the author summarized the pathogenesis and treatment of NPM with traditional Chinese medicine from the perspective of substance exchange channel disturbance, hormone disorder, bacterial infection and immune abnormality, aiming to provide reference and inspiration for the selection of reasonable clinical diagnosis and treatment plans.***

Keywords: Non-lactation mastitis, Pathogenesis**.**

1. Introduction

Non-puerperal mastitis (NPM) is a benign suppurative disease of the breast, which occurs in non-lactating and non-pregnant women. The main clinical symptoms are breast mass, nipple discharge, local redness and pain, skin ulceration, which is difficult to cure and forms fistula and sinus over time. The incidence of this disease can account for 1.0%~ 5.4% of breast diseases in the same period, and the incidence has increased significantly in recent years and gradually shows a trend of younger patients. Through the observation of various clinical cases, it is not difficult to find that the disease has unknown etiology, easy to be confused with breast cancer, easy to miss diagnosis, misdiagnosis or delayed diagnosis, there is no system, clear treatment plan, mixed efficacy and other problems [1]. Moreover, the long treatment process of the disease, complex symptoms, easy to repeat and other characteristics also bring great psychological and economic burden to patients. Therefore, it has become an urgent problem to explore its pathogenesis, improve the effectiveness of treatment, and bring better diagnosis and treatment plans for patients.

Western medicine mostly uses anti-infection, hormone therapy, immunosuppressants, surgical resection of the lesion and other treatment means [2]. Steroid hormones are the main treatment for granulomatous lobular mastitis in the Expert Consensus on Diagnosis and Treatment of non-lactating mastitis formulated by the Breast Health Care and Breast Disease Prevention and Treatment Group of the Women's Health Branch of the Chinese Preventive Medical Association in 2016. However, there is no unified standard for the usage and dosage of hormone therapy, which is prone to side effects such as Cushing's syndrome, weight gain, gastrointestinal reactions and so on. In addition, surgical resection of the lesion is also the main treatment means, but if the scope of surgery is too small, there will be shortcomings such as incomplete clearance of the lesion and easy recurrence. If the scope of surgery is too large, it will lead to the appearance of the breast, lactation function damage, surgical scar is too large and other problems. Staging operation is a great test for patients' economic ability and mental health. With the change of disease treatment mode, traditional Chinese medicine treatment method has gradually entered the public field of vision, and its clinical efficacy and advantages are gradually recognized by the public. Traditional Chinese medicine has long been aware of NPM, and named it "mastitis, mammary sputum, mammary flower, mammary swelling, mammary leakage" according to its characteristics and causes. In the mid-1980s, Professor Gu Bohua named the disease as "comedogenic mastitis", which was later included in "Practical Chinese Medicine Surgery" and is still in use. Through its overall review and syndrome differentiation, traditional Chinese medicine has played its unique advantages in the treatment of NPM, such as short course of treatment, little trauma, little pain, low price, low recurrence rate, and not easy to destroy the appearance and function of the breast. Many scholars have conducted relevant studies on the pathogenesis of NPM and the treatment of traditional Chinese medicine. Based on this, the author summarized the pathogenesis and TCM treatment of NPM from the perspectives of substance exchange channel disorders, hormone disorders, bacterial infection, and immune abnormalities, aiming to provide reference and inspiration for rational selection of clinical diagnosis and treatment.

2. The Pathogenesis of NPM

2.1 The Mechanism of Substance Exchange Channel Disturbance in the Pathogenesis of NPM

2.1.1 Ion channels

Ion transporters play an important role in milk secretion,

maintaining acid-base balance and regulating ion transport in mammary gland cells. The NA-K-Cl- and NA-K+ cotransporters on the basolateral membrane within mammary epithelial cells enable an electrochemical gradient of K+, Cl-, and Na+ to maintain negative charge within the cell relative to lumen contents (usually milk within the mammary gland) [5]. Cellular fluid transport is increased through +the action of the Na-K-+Cl- cotransporter. Related studies have shown that inflammation can cause swelling of the interstitium and cells of various tissues by driving ions and water transporters.

Ion channels are involved in immune regulation and are expressed in large numbers in immune cells. It was found that Ca^{2+} channel is an important regulator of mammary gland development. transient receptor potential vanilloid 6, a calcium-selective channel TRPV6 (transient receptor potential vanilloid 6, The absence of TRPV6 could lead to the destruction of epithelial integrity and the abnormal three-dimensional morphology of acines.

The Piezo1 channel, which acts as a mechanical sensor mediating the development of chronic inflammation, is also involved in the pathogenesis of NPM. Trauma is one of the most common causes of NPM. Many NPM patients suffer from external impact. Piezo1 channel in the mammary epithelial cells is activated after breast compression. The activation of the channel triggers the extracellular Ca2+2+ flow in the mammary epithelial cells and the release of Ca from the calcium pool to transduce inflammatory signals, leading to inflammation. This channel can also sense the changes of local mechanical forces in inflamed tissue and participate in the development of inflammation [7]. Destructive mechanical forces on cells induce the secretion of pro-inflammatory factors, which on the one hand clear out dead tissue cells and on the other destroy normal tissue. When stimulated by inflammatory factors, local blood vessels will undergo a brief contraction, and then through nerve reflex, blood vessels will dilate, increase blood vessel permeability, and intravascular fluid will leak through the blood vessel wall to the outside of the blood vessels, forming local edema. Edema will produce persistent harmful mechanical force, and then damage the tissues, forming a vicious cycle, leading to the prolonged course of NPM disease.

2.1.2 AQP

Studies have confirmed that AQP1, 3, and 5 are present in human breast tissue. Located in the apical and basolateral membranes of endothelial cells in capillaries and venules, AQP1 plays a transport role in moving water from the blood to the interstitial space. AQP1 can regulate rapid swelling dynamics and plays a key role in triggering and accelerating regulatory volume, a process by which cells adjust the volume of thin A cells in response to swelling [9]-[10]. AQP3 is located in the basolateral membrane of acinar and ductal epithelial cells and can transfer water and/or glycerol from the interstitial fluid into the cytoplasm. NPM masses tend to form rapidly and often liquefy and ulcerate in a short period of time, which is associated with cell or interstitial edema caused by AQP transporting water and blood and causing rapid changes in water flow.

M2-type macrophages are involved in the repair and fibrosis of injured tissues, and their continuous expression may be related to the long-term injury of PCM tissues and the prolongation of inflammation. AQP1 and AQP3 participate in macrophage migration and phagocytosis by affecting the volume of macrophages [15]. AQP3-mediated uptake of intracellular hydrogen peroxide (H2O2) is required for NF-κB cell signaling and macrophage activation. AQP3 inhibition or silencing can block LPS initiation and reduce the production of inflammatory factors.

Lactation is a complex process involving the transport and secretion of multiple substances. There are five main known secretory pathways in the mammary gland secretory epithelium: (1) Membrane pathway: Some substances can pass directly through the cell membrane, such as water, urea, glucose, sodium ions (Na^+), potassium ions (K^+), and chloride ions (Cl^-); (2) the Golgi pathway: secretions are transported or sequestrated by the Golgi apparatus and then secreted into the milk duct by exocytosis. Examples include casein, whey protein, lactose, citrate, and calcium; (3) the milk-fat pathway: milk fat globules or some cytoplasmic components, such as milk fat, fat-soluble hormones and drugs, and some unknown growth factors, extruded from the tip of secretory cells surrounded by membranes (milk fat globule membranes); (4) endocytosis: vesicle transport involving various organelles and possibly the Golgi pathway in some cases; and (5) paracellular pathway: direct entry of interstitial fluid into the milk. In pregnancy glands, the paracellular pathway is open, allowing for the transfer of molecules as large as intact immunoglobulins [19]. In fully lactating glands, this pathway is closed, providing a tight barrier between the milk and the interstitial space. During mastitis and degeneration, this barrier opens again.

Studies have found that non-lactating mastitis patients have lipid-like secretions in the mammary ducts, adipose tissue plays an important role in the mammary glands, and lactating mammary glands synthesize large amounts of triglycerides and have a significant need for glycerol. Hydroglycerol channel proteins (AQP3, AQP7, AQP9, and AQP10) are key glycerol channels that allow glycerol to cross cell membranes. The expression of AQP3 in the alveolar MEC is thought to be involved in the uptake of water and glycerol from plasma to produce milk. Fat cells are the main source of glycerol, which is released during lipolysis and is metabolized by other tissues through a carefully planned process. Adipose AQP is a key player in adipose tissue biology, acting on adipocyte proliferation and differentiation and fat deposition. This further confirms that AQP mediates the occurrence and development of NPM to a certain extent.

2.2 The Mechanism of Hormone Disturbance in the Pathogenesis of NPM

2.2.1 Prolactin

Prolactin (PRL) is a polypeptide hormone secreted by prolactin cells in the anterior pituitary gland. Its main functions are lactation, promoting mammary gland development and regulating immune function. It is normally found in low levels in the blood of non-pregnant and non-lactating women [20]-[22]. Abnormally elevated PRL levels may be related to a variety of factors, including

physiological factors (such as stress, sleep, sexual activity, etc.), pathological factors (such as pituitary adenoma, hypothyroidism, polycystic ovary syndrome, etc.), medications (such as antipsychotics, antidepressants, etc.), and other endocrine disorders.

PRL plays an important role in the pathogenesis of NPM, but the specific mechanism is still unclear. Relevant studies have shown that high levels of PRL can lead to mammary duct dilation and increased mammary duct secretion, and antigen substances enter the interlobular stroma, triggering autoimmune reactions [24]. PRL can activate the NF-κB signaling pathway in mammary epithelial cells to produce TNF-α, IL-6 and other pro-inflammatory factors, which can trigger T-cell-mediated immune response and granuloma formation.

Relevant studies have shown that NPM patients with hyperprolactinemia caused by pituitary masses gradually improve the symptoms of mastico-related inflammatory changes after surgical resection and the course of the disease is relatively shortened. Saraiya [26] et al. also found that NPM symptoms can be improved after normalizing PRL levels. Meng [26] Zhao et al. concluded that BMI≥24 kg/m^2, nipple retraction and PRL level increase were high risk factors for NPM through the nomogram.

2.2.2 Ovarian hormones

Fluctuating ovarian hormone levels are another mechanism of NPM pathogenesis. Decreased ovarian function, hormone level changes can cause milk duct wall relaxation, myoepithelial cell systolic function decreased, hinder the discharge of milk duct secretions, induce periductal inflammatory cell infiltration. A number of studies have found that the proportion of long-term oral contraceptives in GLM patients is higher than that in normal women, and drug-mediated changes in hormone levels promote breast acinar secretion, thus participating in the development of the disease.

Obesity can affect the expression of aromatase in mammary adipose stromal cells and stimulate the production of ER to further promote inflammation. Therefore, the change of hormone level plays an important role in the pathogenesis or exacerbation of NPM. The hormone-immune-NPM axis may be one of the etiologies of NPM, but its specific mechanism still needs to be further clarified.

2.3 Mechanism of Bacterial Infection in the Pathogenesis of NPM

The onset of NPM may be related to bacterial infections in the ducts of the breast, especially some special types of corynebacterium, which may activate immune cells and produce exotoxins, thus triggering an inflammatory response. In addition, the study by Professor Yu Zhigang [27] 's team at the Second Hospital of Shandong University showed that the Elfampicin-based triple drug therapy for non-lactation mastitis achieved a high objective remission rate, which provides new evidence-based medical evidence for the treatment of bacterial infections.

2.3.1 The mechanism of bacterial infection in the pathogenesis of granulomatous lobular mastitis

Studies have shown that bacterial infection, especially corynebacterium infection, is closely related to granulomatous lobular mastitis. In multiple studies, kroppenstedtii. corynebacterium has been frequently detected in specimens from patients with granulomatous lobular mastitis, suggesting that this bacterium may be an important factor in the disease.

Corynebacterium Kroppenstedtii. is a gram-positive, lipophilic corynebacterium, and its growth in breast tissue may be related to the fat content of the mammary glands. The bacterium is difficult to grow on normal media, but does well on blood plates, which explains why conventional pus culture results are often negative [29]. Antibiotic therapy and antituberculous therapy may achieve better results in granulomatous lobular mastitis, which may be associated with kroppenstedtii. The properties of corynebacterium are related.

Although bacterial infections are closely associated with granulomatous mastitis, there is currently insufficient evidence to prove that a bacterial infection or a specific bacterium directly causes granulomatous lobular mastitis. In addition, patients with granulomatous lobular mastitis may develop autoimmune symptoms, such as erythema of the lower extremities, arthritis, etc., which are not well treated with antibiotics alone, and the specific mechanisms are still unclear.

2.3.2 Mechanism of action of bacterial infection in the pathogenesis of plasma cell mastitis

Studies have shown that mycobacterium is closely related to plasma cell mastitis, especially non-tuberculous mycobacterium. In the nipple discharge of patients with plasma cell mastitis, the positive rate of bacterial culture is higher, and more studies have shown that the relationship between mycobacterium and plasma cell mastitis is more close.

There are many kinds of mycobacterium, which can be divided into mycobacterium tuberculosis complex group, non-mycobacterium tuberculosis and mycobacterium leprae. The inflammation caused by these bacteria usually manifests as chronic inflammation. In pathological specimens of plasmacytic mastitis patients, the infection of the L type of TB bacteria has been found by means of modified acid-fast staining and immunohistochemical staining. The incidence of non-tuberculous mycobacterium infections is on the rise, and most of them have the capacity of opportunistic infection in humans [28]. In plasmacytic mastitis patients, the widespread use of glucocorticoids and broad-spectrum antibiotics has greatly increased the possibility of opportunistic infections such as non-tuberculosis mycobacterium infections.

Current studies only show that non-tuberculosis mycobacterium may be involved in the occurrence and development of PCM, but it is not certain that it is the main cause of the disease. With the development of detection technology, especially the application of molecular biological techniques, such as GeneBank [30] and other open gene

database for rapid detection and identification of mycobacterium genes, will help to improve the diagnostic accuracy of whether there is mycobacterium infection in PCM. Feng Xinyu [30] conducted a retrospective analysis of the data of non-lactation mastitis patients by Logistic analysis method, and found that bacterial infection was the common factor of granulomatous mastitis and plasma cell mastitis, but whether bacterial infection directly caused the occurrence and development of non-lactation mastitis was still lacking in relevant studies.

2.4 Mechanism of Immune Abnormality in the Pathogenesis of NPM

2.4.1 Immune abnormalities and the incidence of granulomatous lobular mastitis

In 1972, Kessler [30] et al found that the histological features of granulomatous lobular mastitis were significantly similar to those of several autoimmune diseases, such as granulomatous thyroiditis and granulomatous orchitis. Since bacterial culture results were often negative, they proposed that granulomatous lobular mastitis might be an autoimmune disease. Subsequently, Brown [26] et al. proposed that residual postpartum milk may trigger an immune response and local hypersensitivity, resulting in granulomatous lobular mastitis. These ideas gradually gained widespread acceptance and influenced clinical treatment strategies. Adams [28] et al. further found that patients with granulomatous mastitis were often accompanied by erythema in both lower extremities, a symptom that supports the role of autoimmune mechanisms in the development of the disease. Erythema nodosa is a common sign of rheumatic disease that may be caused by delayed allergic reactions to certain pathogens, medications, inflammation of the gastrointestinal tract, or malignancy. Although studies have shown that granulomatous mastitis and IGG4-associated disease (IGG4-RD) are two different diseases, Ogura [28] et al., by studying granulomatous mastitis tissue, found a large number of IGG4-positive plasma cells and CD4 or CD8-positive lymphocytes, as well as an elevated level of IgG4 in the serum of one patient. Which are all common features of autoimmune diseases. Bercot [30] et al. proposed that mutations in the NOD2 gene may lead to neutrophil dysfunction, which may be a factor in susceptibility to granulomatous mastitis. Despite these findings, whether granulomatous mastitis is entirely an autoimmune disease is currently a matter of debate in the medical community.

Therapeutically, glucocorticoids are widely used for granulomatous mastitis and have shown high efficacy. Studies have shown that glucocorticoid therapy is 77% effective, while antibiotics alone are only 5% effective. Akahane [28] et al. suggest that glucocorticoid therapy is the preferred option for granulomatous mastitis. Since glucocorticoids are immunosuppressants, their efficacy in the treatment of autoimmune diseases is significant, which also supports the association of granulomatous mastitis with autoimmune mechanisms.

2.4.2 Immunological abnormalities and onset of plasma cell mastitis

The pathological features of plasmacytic mastitis include a large local infiltration of plasma cells, lymphocytes, and foam cells. These findings indicate that the disease is closely related to autoimmune processes. In 1958, Patey and Thackray [30] proposed that plasmacytic mastitis is a type of aseptic inflammation with a possible mechanism of abnormal extension of squamous epithelial cells at the opening of the milk duct to the inner wall of the milk duct, leading to obstruction of the lumen by keratinized detritus and lipid secretions, causing inflammation. The study of Wenhua [32] Song et al. showed that nipple retraction may lead to dilation of milk duct and damage of epithelial integrity, which in turn leads to leakage of lipids and antigenic reaction of surrounding tissues, leading to infiltration of chronic inflammatory cells. The presence of CD20 and CD45RO-positive lymphocytes in the breast tissue of patients with plasmacytic mastitis was found by immunohistochemistry by Guo Shuang [30] ping et al., supporting the idea that the disease is an autoimmune disease. Houqi Sun et al. found that the expression level of IL-2 in plasmacytic mastitis was significantly higher than that in the hyperplasia group, while the expression of IL-4 was not statistically significant, suggesting that Th1 cytokine IL-2 may play an important role in the occurrence and development of the disease.

In terms of treatment, plasma cell mastitis is usually treated with immunosuppressive agents such as glucocorticoids, and sometimes combined with antibiotics. A recent study by Wang et al. indicated that the expression levels of NF-κBp65 protein and ICAM-1 protein were significantly increased in plasma cell mastitis tissues, which may be related to the high expression of NF-κBp65 protein and the subsequent upregulation of ICAM-1 protein after the mammary duct was stimulated by external inflammation, leading to lymphocyte infiltration.

Although non-lactation mastitis has been shown to be associated with autoimmune processes, no specific autogenic component leading to immune system disorders has been identified. Rui Xu et al. further supported the association between non-lactating mastitis and autoimmune diseases by detecting serum antinuclear antibodies (ANA) and antihistone antibodies (AHA) in non-lactating mastitis patients, and found a higher positive rate of ANA and AHA. Autoimmune diseases are usually caused by the immune system's reduced tolerance or destruction of its own components, but current research has not fully elucidated the specific pathogenesis of non-lactating mastitis, which is one of the reasons why the disease is controversial [30]. Therefore, the mechanism of action of autoimmunity in non-lactation mastitis still needs further study.

3. Treatment of Traditional Chinese Medicine

The treatment of comedogenic mastitis should follow the treatment principle of "elimination, support and supplement", that is, different treatment strategies should be adopted at different stages. In the stage of mass formation, the main method of dissipation; When abscess is formed, supplement or permeation method is adopted; And in the late stage of ulceration, the supplementary method is mainly used.

3.1 TCM Internal Treatment Method

Hidden stage: This is the early stage of the disease, patients may feel breast tenderness and mood swings, red tongue, yellow fur, pulse slip. At this time, the treatment is mainly to clear the liver heat, eliminating phlegm and removing dampness.

Mass stage: this stage of treatment focuses on soothing the liver and promoting blood circulation, reducing swelling and dispersing knot, the commonly used drugs include bupleurum, Dangica, red peony, salvia miltiorrhiza and so on.

Abscess stage: the treatment goal is to tori through pus, and ying to reduce swelling, leading to evil out, the commonly used drugs are bupleurum, Yujin, white flower snake's tongue and so on.

Fistula stage (later stage of ulceration): The treatment is mainly supplemented, supplementing qi and invigorating spleen, promoting blood circulation and removing fat, and promoting healing.

3.2 Traditional Chinese Medicine External Treatment

Non-collapse period: including mass period, abscess unbroken period and late treatment of stiff block period. Choose different drugs according to the Yang or Yin swelling, such as Golden yellow paste, Qingdai powder or Yang and coagulation paste.

Has ulcerated stage: ulceration late form fistula, sinus, can use Wuwu Dan, Jiuyi Dan external application, promote the removal of saprophylaxis new.

Fire needle treatment: suitable for comedogenic mastitis acute pyogenic period, the use of warm effect to remove cold dampness, remove rot and discharge pus, dredge meridians, diffuse knots and detumescence. During operation, avoid areola, form smooth channel, and promote pus drainage.

3.3 Thread Hanging Method

Thread the silk thread through the silver probe, enter from the outer opening of the sinus, protrude from the large catheter of the nipple, and gradually tighten until the thread cuts the sinus. At the same time with traditional Chinese medicine preparation to promote wound healing.

The improvement of surgical methods of traditional Chinese medicine, such as wound expansion and nipple correction, shows that external treatment plays an important role in the treatment process. The key is to identify the stage of disease by different clinical manifestations and to treat it dialectically. The TCM internal and external treatment methods are combined to give full play to their respective advantages and jointly promote the recovery of diseases.

4. Conclusion

NPM is a chronic breast disease that is difficult to completely cure and prone to recurrence, and the treatment of this disease is a major challenge for patients and their treating physicians. Existing studies have shown that NPM may be related to substance exchange channel disorders, hormone disorders, bacterial infections, and immune abnormalities, but the specific mechanism is not clear and needs further study. In recent years, the advantages of traditional Chinese medicine in the treatment of non-lactation mastitis have become increasingly prominent. However, the key to shorten the course of disease is to distinguish the various stages of disease development and rationally select treatment methods.

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