Article published online: 2024-09-30

Correlation Between Granulomatous Mastitis and Autoimmune Function and the Immune-regulating Role of Traditional Chinese Medicine

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CMNP 2024;4:e88–e92.

Abstract

Granulomatous mastitis (GM) is a benign granulomatous condition, and its pathogenesis may be related to autoimmune disorders. Cellular immunity, humoral immunity, immunoglobulins, and complement could all play a role in the disease process, showing certain clinical patterns. Corticosteroids can quickly control disease progression, and immunosuppressants can be used for complex and refractory GM cases. In traditional Chinese medicine (TCM), "healthy qi" is similar to immune system function. For GM with deficient healthy qi, TCM treatments such as internal and external herbal applications can help regulate immune function and shorten disease duration by staged and TCM treatment, regulating viscera, reinforcing healthy qi, and eliminating pathogenic factors.

Keywords
- granulomatous mastitis
- TCM
- immune regulation
- TCM treatment
- staged treatment

Granulomatous mastitis (GM), also known as granulomatous lobular mastitis, is a benign, challenging breast disease predominantly occurring in non-lactating women. Its causes are often autoimmune responses, pituitary lactogen secretion abnormalities, and infections by *Corynebacterium*, with studies suggesting it is a specific autoimmune disease.[1] Traditional Chinese medicine (TCM) plays a significant role in treating GM, and this review explores the relationship between GM and immune function, as well as TCM's key role in regulating immune function.

Immunological Pathogenesis of Granulomatous Mastitis in Modern Medicine

GM is characterized by non-caseating granulomatous inflammation centered on lobular necrosis, with acute and chronic inflammation of the breast, accompanied by small abscesses and foreign body granulomas.[2] Studies have found GM to be an autoimmune disease with immune dysfunction, manifesting as nodular erythema of the lower limbs or arthritis in patients.[3] Corticosteroids and cytotoxic drugs can alleviate the clinical symptoms of this disease.[4,5] Yu et al[6] found that during the disease process of GM, there is a disorder in T-cell subsets and a relative decrease in $CD4^+$ T cells. There may also be a weakened promoting effect of $CD4^+$ T cells on protective $CD8^+$ T cells, leading to excessive killing by $CD8^+$ T cells, which causes immune dysfunction and results in persistent GM. Xu et al[7] detected abnormalities in immunoglobulins and complement levels in the peripheral blood of patients, with high positivity rates for antinuclear antibodies and antihistone antibodies, revealing it as an autoimmune disease with immune dysfunction. Immune-related pathways and proteins have been confirmed to be involved in the disease process. Zhao et al[8] discovered that excessive activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway and immunoglobulins were closely related to the

received
April 1, 2024
accepted after revision
June 12, 2024

DOI https://doi.org/10.1055/s-0044-1790539.
ISSN 2096-918X.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

development of GM. The observation group showed significantly reduced levels of IgA, IgM, and IgG, indicating that immunoglobulins are closely related to the development of GM.

Additionally, as research related to immunology increases, GM can be further classified or identified based on immune indicators. Research by Ogura et al[9] divided GM into IgG4-related and non-IgG4-related types. Kong[10] found that IgG4 expression levels were significantly higher in GM patients with nipple retraction compared with those without retraction, suggesting that the two may represent different clinical subtypes of GM. Lai et al[11] divided patients into abscess and non-abscess groups. They found that, compared with the non-abscess group, the abscess group had higher levels of C-reactive protein, erythrocyte sedimentation rate, prolactin, interleukin (IL)-2 (IL-2), IL-8, IL-6, as well as increased levels of NOD-like receptor pyrin domain-containing 3 (NLRP3), the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), caspase-1, and IL-1β in breast tissue. This indicated a more active inflammatory state and stronger inflammatory response in abscess-type patients. Combined detection of NLRP3, ASC, caspase-1, and IL-1β can effectively enhance the differentiation between abscess and non-abscess types. It is evident that immune cells, immune-related pathways, and immunoglobulins are all involved in the occurrence and development of the disease and can be used for staging and classification through immunological indicators.

Modern Medical Immunotherapy for Granulomatous Mastitis

The primary treatment for GM involves glucocorticoids and immunosuppressants, especially for acute patients, which shows significant effectiveness. In clinical practice, prednisone is used at a dose of 0.75 $mg \cdot kg^{-1} \cdot d^{-1}$, while the initial dose of methylprednisolone tablets is 20 $mg \cdot d^{-1}$, which can be gradually reduced after symptom relief until clinical symptoms are completely resolved or stabilized.[12] Attention should be paid to potential adverse effects of hormone therapy, such as hypercortical syndrome, gastroduodenal ulcer, and worsening infections.[13]

In clinical settings, low-dose hormones can be used to reduce adverse effects. One study administered oral prednisone acetate tablets at a dose of 0.4 $mg \cdot kg^{-1} \cdot d^{-1}$, starting treatment for 4 weeks, then reducing by 2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ from the fifth week until a dose of 5 $mg \cdot kg^{-1} \cdot d^{-1}$ was reached, which was maintained for 2 weeks before discontinuation. The study found that low-dose prednisone therapy had similar efficacy to recommended doses, with no significant differences in efficacy, postoperative complications, or recurrence rates but had a lower incidence of adverse effects compared with the control group.[14] Additionally, topical glucocorticoids can be used to minimize drug-related adverse effects, increase patient compliance, and improve treatment efficacy. One study compared multiple-point injections of triamcinolone at the lesion base with oral methylprednisolone and found that local hormone injection significantly shortened the treatment course compared with oral hormone therapy.[15] To enhance clinical efficacy, combining hormones with other treatment modalities can achieve the best clinical outcomes and safety. Chai[16] combined dexamethasone with surgery for GM treatment, which significantly reduced pain scores and improved postoperative breast appearance satisfaction. Some studies combined hormones with TCM treatment to control inflammation and regulate autoimmunity, which could better reduce the adverse effects of hormones and achieve good clinical efficacy.[17–20]

Immunosuppressants like methotrexate (MTX) are often used for refractory GM with a clear pathological type. The dosage and treatment duration of MTX are not yet well-defined, with clinical recommendations ranging from 7.5 to 20.0 mg per week,[12] and it must be combined with oral folic acid to prevent drug adverse effects. One study involving 33 female patients, most of whom had failed antibiotic, prednisone, and surgical interventions, showed that 94% of patients improved after 15 months of MTX monotherapy, indicating MTX is an effective treatment for refractory GM.[21] Dalbaşı and Akgül[22] used MTX at a weekly dose of 15 mg combined with methylprednisolone at 8 mg daily and retrospectively included 62 patients. These patients had an average clinical and radiological remission period of 3 to 14 months, with a recovery rate of 93.71% during follow-up. Tian et al[23] included patients resistant to corticosteroids and treated with MTX, suggesting that considering MTX and low-dose corticosteroids as alternatives for corticosteroid-resistant GM patients. Postolova et al[21] showed that if MTX treatment is effective, corticosteroids can be gradually reduced and discontinued. MTX is generally not recommended as an initial treatment in domestic guidelines and is typically used for refractory GM, with limited experience and research on MTX treatment in China.

Etiology and Pathogenesis of Granulomatous Mastitis in TCM

GM falls under the categories "acne-like mastitis" and "granulomatous mastitis" in TCM. The onset of the condition can be attributed to external trauma or dietary irregularities as a foundation for the disease. Additionally, liver qi stagnation leads to qi stagnation and blood stasis, which accumulates in the breast collaterals, or liver failing to act freely and stomach failing to descend causing accumulation of phlegm and dampness, or kidney yang deficiency leading to inability to warm and phlegm-stasis accumulation, can all contribute to the development of GM.[24–27] Li et al[28] believe that according to *yin–yang* syndrome differentiation, GM can be divided into *yin* syndrome, *yang* syndrome, and half-*yin* and half-*yang* syndrome.

Although the term "immunity" is not used in TCM, "Zheng qi" (healthy qi) is equivalent to the body's immune function. An imbalance of healthy qi and invasion of pathogenic qi indicate immune dysfunction and lead to disease. TCM treatment of GM is guided by "treating both internally and externally" and "treatment based on syndrome differentiation," which can achieve good clinical results.

TCM Treatment of Granulomatous Mastitis and Its Immune Regulation Effects

Internal Treatment in TCM

Internal treatment in TCM focuses on staged treatment and syndrome differentiation. Clinically, GM is categorized into mass type, abscess type, and post-ulceration type, with treatment based on clinical characteristics in different stages and syndrome differentiation. The mass stage primarily focuses on "reducing," including clearing heat and reducing swelling or warming *yang* and reducing swelling. The abscess stage uses the "lifting method," including draining pus, benefiting qi to expel toxins, and warming *yang* to expel toxins. The post-ulceration stage uses "nourishment," including benefiting qi and strengthening the spleen, warming *yang* and reducing swelling, and benefiting qi and nourishing blood.[29] Based on this, various TCM practitioners approach GM from different angles. Zhang[30] believed that this disease was located in the nipple and breast, and it was internally attributed to the liver and stomach and closely related to liver qi stagnation and stagnated liver qi transforming into fire and affecting the spleen and stomach. Treatment should focus on liver fire attacking the stomach dispersing the liver and clearing the stomach.

Pei[31] proposed that phlegm, heat, blood stasis, and stagnation are the main pathogenesis, with phlegm–damp–heat obstructing the breast collaterals, causing qi stagnation and blood stasis, and transforming into heat toxins rotting flesh to pus and eventually forming GM. Treatment methods include warming to promote pus drainage, clearing to promote pus drainage, tonifying to promote pus drainage with the use of herbs with effects of dispersing the exterior, clearing and purging combined with external treatments to expel pathogens, promote pus discharge, benefits qi and nourish the blood to promote granulation, and prevent a recurrence. Wang[32] introduced the "clearing and elevating method" for treating GM abscesses, emphasizing the use of the Fangfeng (Saposhnikoviae Radix)–Huangqi (Astragali Radix) herbal pair to reduce swelling, dissolve masses, and expel toxins and pus. Deng et al[33] believed that the pathogenesis involved an external invasion of the Xuanfu (sweating pores) causing obstruction; or the deficient or impaired Xuanfu (sweating pores) was contacted with external pathogenic toxins, which caused an internal generation of phlegm turbidity, and static toxins adhering to the breast collaterals and led to damage and loss of nourishment to the breast collaterals. Based on the "Xuanfu (sweating pores)–collaterals" theory, early treatment should focus on penetrating the exterior and opening the Xuanfu (sweating pores); in the middle stage, remove turbidity and open the Xuanfu (sweating pores), providing a route for pathogenic qi to exit; and in the later stage, for chronic disease involving collaterals, deficiency and impairment of the breast collaterals, treatment should focus on tonifying deficiency and unblocking collaterals, warming the breast collaterals with *yang*-warming method. Lyu[34] suggested using the method of harmonizing *yin* and *yang* and the gradual lifting method, which means applying a half-reducing, half-nourishing lifting method in cases of half-deficiency and half-excess or half-*yin* and half-*yang* syndrome. Some studies suggested that kidney function was similar to the immune system in modern medicine,[35–38] and proposed that treatment of GM should emphasize nourishing and stabilizing the kidney, enriching kidney essence, and combining tonifying the kidney, benefiting the lung, dispersing the liver, and tonifying the spleen to regulate the function of the three organs and adjust immune function from the source of the disease.[39]

Some research showed that internal use of Chinese herbs helps regulate immune function in patients, promote the resolution of lumps, drainage of abscesses, and formation of fistulas. A study by Fang et al[40] found that minimally invasive debridement combined with qi-benefiting and nutrient phase-nourishing herbs can reduce rebound and recurrence rates, shorten disease duration, alleviate patient suffering, and correct immune imbalance in GM patients. Liu et al[41] used network pharmacology and molecular docking to explore the mechanism of Tounong Powder in treating GM, and indicated that it regulated GM immune-inflammatory responses through multiple components, targets, and pathways. Clinical studies validated its efficacy and IL-6-centered immune-inflammation regulation. Xie et al[42] found significantly higher levels of $CD3^+$, $CD4^+$, $CD8^+$, and $CD8^+$, $CD28^+$ T cells in GM patients' blood, inhibited expression of $CD4^+$ $CD25^+$ T cells. Compared with those with liver meridian stagnated heat syndrome, patients with phlegm–damp–heat syndrome showed increased $CD3^+$ T cells and higher IgG levels, which indicated a correlation between TCM syndromes and autoimmune function.

From a modern pharmacological perspective, Chinese herbs used to treat GM all have the effects of regulating inflammatory cytokines and correcting immune dysfunction. Commonly used herbs include Zaojiaoci (Gleditsiae Spina), Danggui (Angelicae Sinensis Radix), Pugongying (Taraxaciheraba), Chaihu (Bupleuri Radix), and Chishao (Paeoniae Radix Rubra), and they are often used in pairs.[43] Research discovered that saponins of Zaojiaoci (Gleditsiae Spina) produce cytokines like interferon and interleukins to enhance immune stimulation and serve as immune adjuvants[44] while also having strong anti-inflammatory effects.[45] Chaihu (Bupleuri Radix) had anti-inflammatory and analgesic effects, and its saponins also had anti-inflammatory effects.[46] Data mining and network pharmacology methods have identified key active components of the medical pair of Jinyinhua (Lonicerae Japonicae Flos) and Lianqiao (Forsythiae Fructus), such as quercetin, luteolin, and wogonin, with key targets of TNF, IL-6, IL-1β, and in GM, and concluded that the core medical pairs may exert therapeutic effects by regulating IL-17 signaling, Toll-like receptor signaling, and TNF signaling pathways.[47]

External Treatment in TCM

Gong et al[48] believed that *yang* deficiency is the fundamental pathogenesis of GM. Cotton padding was used to "assist the sore to restore *yang*" by keeping the wound warm and promoting qi and blood flow to aid in the discharge of pus and healing. Liu[49] advocated for a combination of

acupuncture and medicine for GM. Liu proposed that treatment should be based on the clinical characteristics at different stages; after the formation of pus, use fire needling method to draw heat with heat and expel toxins; in the post-ulceration stage, use fire needling to warm and dredge the meridians, remove necrotic tissues and promote granulation; in the scar stage, for breast scar hyperplasia, use fire needling to promote qi and blood flow, attack and disperse the masses. Ying and Guo[50] employed local pricking and cupping combined with hormone treatment for GM with lumps and showed that the combination was more effective than hormone treatment alone. Tang[51] used Badu Shengji Powder with main medicinals of Bingpian (Borneolum Syntheticum), Luganshi (Calamina), and Longgu (Os Draconis) for the treatment of sinus tract pus, which resulted in significant improvement in systemic and local symptoms and obviously reduced IL-1β expression in breast granulation tissue. Therefore, external TCM treatment primarily uses staged approaches, including topical application of herbs, incision and drainage, cotton padding, medicated threads or gauze, moxibustion, and acupuncture, to rapidly address the disease site, dissipate or drain local visible pathogens, reinforce the body's healthy qi and expel pathogens to achieve a remarkable therapeutic effect on GM and meanwhile regulate immune function by intervening the expression of inflammatory factors.

Conclusion

The occurrence and development of GM are related to various immune cells, cytokines, immunoglobulins, and complements, with a close connection between immune dysfunction and the disease. The disease has a long course and is difficult to cure, prone to recurrence. Corticosteroids can rapidly control disease progression. For complex and refractory GM, immunosuppressants may be used but attention must be paid to the adverse reactions of both treatments. In TCM, the pathogenesis of GM can be attributed to internal factors such as deficiency of innate constitution and kidney qi deficiency, combined with external pathogenic invasions, which leads to qi stagnation and blood stasis, formation of lumps, necrotic tissues, and pus. For GM with deficient healthy qi, TCM treatments such as internal administration and external applications can help regulate overall immune function and accelerate the absorption of inflammation by staged and simultaneous internal and external treatment, regulating viscera, reinforcing healthy qi, and eliminating pathogenic factors. Chinese medicine has the effects of regulating and improving the body's immune function. Therefore, regulating immune function is a new approach to the prevention and treatment of GM, and the TCM principle of "simultaneous internal and external treatment" is of great significance in correcting the immune imbalance in GM.

CRediT Authorship Contribution Statement

Jiangshan Yuan: writing—original draft, investigation, and conceptualization. **Xufeng Cheng**: supervision, funding acquisition, and writing—review and editing. **Beibei Wang**: supervision and writing—review and editing. **Zepeng Wang**: investigation.

Funding

This work was supported by the 2022 National Clinical Research Base "Top List" Special Project of the Health Commission of Henan Province (2022JDZX086), 2021 National Clinical Research Base Research Special Project of the Health Commission of Henan Province (2021JDZY018), and National Distinguished and Veteran TCM Experts Inheritance Studio Construction Project of the National Administration of Traditional Chinese Medicine (2100601-CZ0175).

Conflict of Interest

The authors declare no conflict of interest.

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