International Journal of Women's Health

Dovepress
Taylor & Francis Group

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REVIEW

Idiopathic Granulomatous Mastitis: Immune-Pathogen Imbalance in a Treatment-Resistant Benign Inflammatory Disease

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Abstract: Idiopathic granulomatous mastitis is a benign non-specific inflammatory disease that occurs in women during non-lactation. Main symptoms in the early stages of disease include red breast lumps, swelling, heat and pain, whereas in the later stages, breast abscesses, sinus tracts, and even ulcers may develop. At present, the etiology and pathogenesis of IGM remains unclear, and there are no standardized guidelines for IGM treatment, which leads to treatment resistance and frequent recurrence, causing serious distress to women's physical and mental health. Based on the existing literature evidence, this paper proposes the "immunity-pathogen imbalance pathogenesis" model, the disease is caused by the imbalance between pathogens and immune system in the breast, resulting in granuloma as the characteristic immune damage response, and Corynebacterium may be the driving factor of the cascade reaction. This article summarizes etiology, diagnostic methods, treatment plans, and recurrence factors, and aims to translate existing mechanisms into a practical clinical framework.

Keywords: idiopathic granulomatous mastitis, etiology, pathogenic bacteria, therapy, antibiotics, methylprednisolone

Introduction

Idiopathic Granulomatous mastitis (IGM) was first described in 1972 by Kessler and Wolloch.[1] IGM is a benign and non-specific inflammatory disease that affects non-lactating females. The etiology of IGM remains unclear. However, several risk factors have been associated with it, including autoimmunity, infections, high prolactin levels, and use of oral contraceptives and psychoactive drugs. Main symptoms in the early stages of disease include red breast lumps, swelling, heat and pain, whereas in the later stages, breast abscesses, sinus tracts, and even ulcers may develop. There are currently no standardized guidelines for IGM treatment. Treatment methods such as hormones, antibiotics, immunosuppressive agents and surgery have been reported. However, these methods either require a long treatment time, prolong course of the disease, or lead to easy recurrence. Consequently, patients may develop scar hyperplasia, hyperpigmentation of the breast skin, and breast deformity, causing significant physical and mental distress.

Epidemiology

Idiopathic granulomatous mastitis, a type of non-lactating mastitis, lacks clear data on its incidence rate, which varies by region. Studies conducted in Germany have shown that mastitis accounts for 3% of benign breast diseases[2] with an annual prevalence of 2.4 per 100,000 women, and an incidence of 0.37%.[3–6] The disease has been frequently reported in China, Turkey, Iran, Spain,[7–13] but infrequently in Europe and in the US. Moreover, the disease primarily affects women who are approximately 30 years old after childbirth,[14] often within five years of ceasing breastfeeding.[15] Idiopathic granulomatous mastitis is rarely reported in men or nulliparous women.[16,17] Most patients have high body-mass index (BMI) and increased prolactin, smoke, and use oral contraceptives. The literature reports that BMI value were ≥30,

Received: 26 April 2025
Accepted: 2 September 2025
Published: 9 October 2025

25–30, and < 25 for 10%, 45%, and 45% of patients, respectively.[14,18] A childbearing history was reported for 93% of patients, whereas 7% had no children.[9,10,15–19] The time from last lactation to disease onset was > 5 years for 12%, and ≤5 years for 88% of patients.[9,14,19–23] 93% of cases present with unilateral breast disease, while 7% present with bilateral breast disease. Fifteen percent of patients had a smoking history, whereas 85% did not smoke.[9,18,19,21,24,25] A history of oral contraceptives was reported for 23% whereas 77% has not used oral contraceptives.[9,18,21,24] Thirteen percent has elevated prolactin levels and 87% had normal levels[14,23] (Figure 1).

Etiology

Autoimmunity

Immune Cells and IGM

Innate immune cells, including macrophages and NK cells, exhibit altered functions in IGM. Macrophage differentiate into M1 and M2 subtypes.[26] M1 macrophages kill microorganisms and promote inflammation,[27] while M2 macrophages secrete cytokines that inhibit inflammation and enable tissue repair.[28] M1 and M2 macrophages can transform into each other and maintain a balance between pro-inflammatory and anti-inflammatory responses to ensure homeostasis.[29] NK regulate immunity via cytokines or cytotoxins that are crucial for immune protection.[30,31] Immunohistochemical studies showed higher expression of M2 (CD68+ and CD163+) macrophages and CD57+ NK cells in IGM versus breast cystic hyperplasia (Figure 2A) IgG4+ plasma cell expression was significantly higher in IGM patients without nipple retraction.[29]

Related studies found that T lymphocytes were predominant in IGM, and a T-cell-mediated reactive inflammation in IGM may be caused by ductal epithelial cell injury and form a lobular-centered granuloma lesion.[10] Subsequent studies further confirmed the dominance of T lymphocytes in the inflammatory microenvironment in IMG, highlighting their importance in IGM pathogenesis.[32] Based on their function, T cells can be divided into T helper (Ths) and regulatory T cells (Treg).[33,34] Treg cells were reported to play a suppressive role in the immune system, and any disruption in the

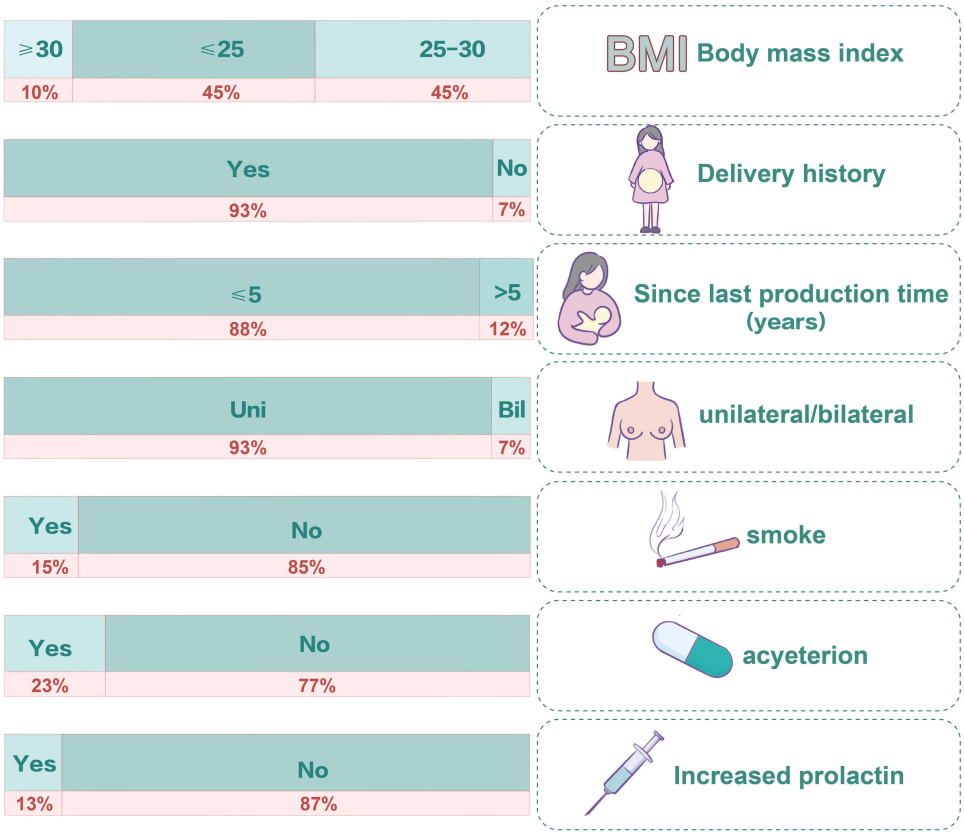

Figure 1 Clinical characteristics of patients with granulomatous mastitis.

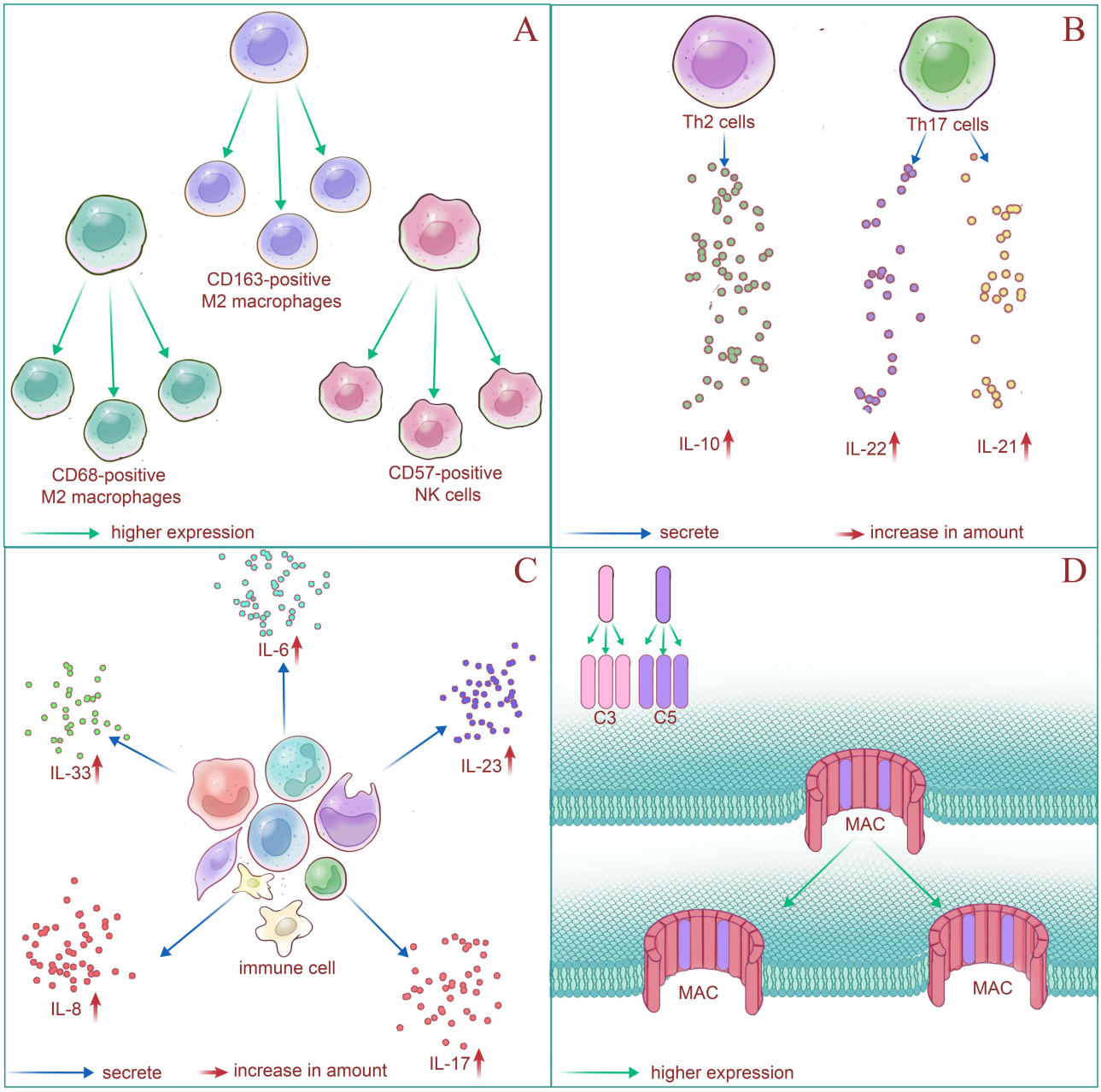

Figure 2 Changes of immune system in patients with granulomatous mastitis: (**A**) The number of CD163-positive M2 macrophages, CD68-positive M2 macrophages and CD57-positive NK cells increased. (**B**) The secretion of IL-10 by Th2 cells increased. The secretion of IL-22, IL-21 by Th17 cells increased. (**C**) The secretion of IL-6, IL-23, IL-17, IL-8, IL-33 increased. (**D**) C3, C5 and MAC numbers increased.

function of Treg cells may cause immune imbalance, and result in immune injury to the body,[35] as in giant cell arteritis (GCA) and other autoimmune vasculitis.[36] Studying exploring differences in Tregs and B cells across IGM subgroups found variation in Treg expression. Specifically, Treg levels differed between the and remission stages of IGM patients as well as between IGM patients and healthy controls. However, there was no significant difference in the regulatory B cell subpopulations.[37] Hence, changes in regulatory T cell subpopulations and quantities appear integral to the immune response of the mammary glands. Another study found that the percentage of lymphocytes, percentage of T helper lymphocytes, and the ratio of CD4/CD8 in the IGM group were lower than those in the healthy control group. The counts and percentages of white blood cells and neutrophils, absolute values of monocytes and cytotoxic T lymphocytes, and the

https://doi.org/10.2147/IJWH.S536970

percentages and absolute values of natural killer cells (NK cells) and natural killer T cells (NKT cells) were also found to be higher than those in the healthy control group.[32]

TREM-1 is a triggering receptor expressed in myeloid cells. In autoimmune disorders, the expression of TREM-1 in myeloid cells increases,[38–40] promoting the secretion of monocyte chemoattractant protein-1, monocyte chemoattractant protein-3, interleukin-6, interleukin-8, and other pro-inflammatory factors.[38] The level of TREM-1 in IGM patients was found to be higher than that in the normal control group in both the active and remission stages.[38]

Cytokines

Cytokines constitute an integral part of immune regulation, produced by immune and non-immune cells, with activated T cells as the main source.[41–44] Cytokines mediate immunity, inflammation,[45,46] and immune injury. In previous studies, levels of inflammatory cytokines IL-22 (Figure 2B) and IL-23 (Figure 2C) were found to be significantly increased in IGM patients.[47] Moreover, serum interleukin (IL)-6 level in IGM patients was found to be significantly higher than that in healthy controls, and the serum IL-6 and C-reactive protein (CRP) levels in patients with severe IGM were significantly higher than those in patients with mild to moderate IGM.[48] Similarly, the IL-33 and sST2 levels were significantly higher in the IGM group than in the healthy control group.[49]

In another study, IL-10 (Figure 2B), IL-17 (Figure 2C) and IL-8 (Figure 2C), levels in IGM patients were found to be higher than those in healthy controls.[50] IL-17 induces neutrophilia by increasing the expression of granulocyte colony-stimulating factor (GCSF) and responding to neutrophil chemokines.[51] IL-17 also induces chemokine production in lymphocytes, dendritic cells and monocytes.[52] IL-8 is produced by a variety of cells, but is released only under inflammatory conditions.[53] IL-8 also plays a pivotal role in attracting neutrophils to sites of inflammation.[54] Interestingly, IL-10 is mainly produced by Th2 cells yet has a significant negative immunoregulatory effect.[55] HLA-A*10, HLA-A*24:03, HLA-B*18, and HLA-DR*17 frequencies were also found to be high in IGM patients. In addition, the frequencies of HLA-A*10, HLA-A*24, HLA-A*32, HLA-B*18, HLA-B*103, and HLADR*17 were found to be higher in patients with recurrent IGM than in those without recurrence.[56] High frequencies of HLA-A*24:03 and HLA-B*18 may in particular suggesting an association of IGM with humoral and auto immunity.[56]

Complement Activation Mediates Immune Injury

The membrane attack complex (MAC) is the terminal component of the complement activation pathway,[57] which triggers inflammatory response.[58,59] Elevated MAC levels lead to apoptosis and death.[60,61] MAC was reported at elevated levels in the peripheral blood and tissues of IGM patient (Figure 2D), and was considered a key substance causing injury to mammary ductal epithelial cells in IGM.[62] IGM pathology involves the loss of the acinar structure and ductal injury.[63,64] This study confirmed that the abnormally activated complement pathway in patients with IGM increases MAC, which activates other immune mechanisms and causes mammary ductal epithelial cell injury. Another study reported elevated levels of C3/C3a-C3aR and C5/C5a-C5aR1 in IGM tissues[65] (Figure 2D). The increased expression levels of the MAC, C3, and C5 indicate that complement-mediated activation contributes to cell damage in IGM, further evidencing complement-mediated immune injury (Figure 2).

Pathogen Presence

In 1985, a study[66] found that patients with nipple discharge caused by mammary duct ectasia had a higher rates of secretion than those without nipple discharge. Therefore, certain pathogens are considered to be closely-associated with this disease. Corynebacterium was considered the main bacterial flora that causes IGM, as it was detected in 41–60% of patients in previous studies.[67,68] In another study found Corynebacterium in all patients, with 57.89% of whom having Corynebacterium kroppenstedtii.[69] In similar studies, Corynebacterium also had the highest detection rate among other pathogens.[70–72] Corynebacterium is a recognized cause of livestock diseases.[67,73] However, improvements in detection technology revealed the presence of not only Corynebacterium, but also other pathogenic microorganisms and viruses as well. In accordance with a previous report,[19] 24 genera, including Ochrobactrum, Delftia, Streptococcus, and Peptoniphilus (Table 1) were detected in samples. Epstein-Barr virus has been detected in IGM samples[68] (Table 1).

Table 1 Pathogenic Factors of Idiopathic Granulomatous Mastitis

Factors	Type	Detection Method	Ref
Pathogen	Propionibacterium Staphylococcus Corynebacterium Delftia Pseudomonas Streptococcus Finegoldia magna Serratia Fusobacterium Ochrobactrum Peptoniphilus Acinetobacter Prevotella Enhydrobacter Anaerococcus	16S rRNA sequencing	[19]
Pathogen	Epstein-Barr virus Corynebacterium Acinetobacter baumannii Thermophilic bacteria Streptococcus pneumoniae Pseudomonas oleovorans Klebsiella Staphylococcus	Metagenomic Next-Generation Sequencing	[68]

Thus, IGM pathogens usually occur as mixed infections. It remains unclear if the diversity of bacterial genera underlies antibiotic resistance and recurrence in IGM.

The role of infections in IGM remains unclear. Owing to the anatomical structure and function of the mammary gland, certain bacterial flora can be detected in the breast tissue under normal conditions,[74] such as Lactobacillus, Bacteroides, Anaerococcus, Staphylococcus. However the pathogenic role of isolated bacterial species is also not yet clear, complicating distinctions between infection, colonization, and contamination.[75–79] While studies find microorganisms in breast tissue, Corynebacteria – dominant in IGM – constitute a low proportion of normal tissue flora.

Genes and Signal Pathways in Idiopathic Granulomatous Mastitis

Previous studies examined miRNAs expression in tissues IGM patients, finding significantly higher serum miR451a and miR55713p levels than those in healthy individuals.[80] Another study analyzed 12,115 mRNAs, with 207 differentially-expressed (136 upregulated and 71 downregulated) between GM and normal tissues.[81] Overexpressed GM genes also correlated with breast cancer, suggesting that chronic inflammatory stimuli are risk factors for breast cancer. Another study also found that the C677T polymorphism in the methylenetetrahydrofolategene was closely related to granulomatous lobular mastitis.[82]

In some studies,[51] human plasma cell mastitis tissue was converted into an oil emulsion and injected into mice to confer pathological features that were highly similar to those of human plasma cell mastitis. Thus, a mouse model of plasma cell mastitis was established. Later studies injected IL-6 into this model, and found that the IL-6/JAK2/STAT3 signaling pathway was activated. Mice treated with the signaling pathway inhibitor (AG-490) also showed significantly fewer mammary plasma cells and controlled inflammation.[83]

Exosomes are involved in in the regulation of inflammatory responses and immune balance.[84,85] In IGM cells, the expression of exosomes and the activity of the signaling pathways mediated by them are increased. A previous study[86] found that the secretion of exosomes in the PCM was increased, and the PI3K-Akt-mTOR signaling pathway was activated. An injection of an exosome inhibitor (GW4869) to into the PCM mouse model revealed that the structure of

the mammary ducts in mice was improved, and the infiltration of plasma cells and lymphocytes was decreased.[87] Another study demonstrated that exosome MiR-221 derived from mammary epithelial cells mediated the polarization of M1 macrophages through SOCS1/STATs, and promoted the development of local mammary inflammation.[88] These findings on exosomes and signaling pathways provide further evidence regarding the immune injury mechanism in IGM. The inhibition of exosome secretion can significantly inhibit the infiltration of inflammatory cells, and may provide with a viable therapeutic treatment strategy in the future.

Other Factors

Elevated serum prolactin levels, and use of oral contraceptives and psychoactive drugs are considered risk factors for IGM. However, these associations are based on relatively few studies, and the underlying mechanisms are still unclear.[89–91] Prolactin (PRL) is a neuroendocrine polypeptide hormone that stimulates DNA synthesis and epithelial cell proliferation, increases milk yield in the mammary glands, and thus plays a role in the pathogenesis of mastitis.[92] A retrospective study also reported elevated serum prolactin levels in patients with IGM.[68] Two studies[93,94] reported development of IGM in nonpregnant patients due to drug-induced hyperprolactinemia. Previous studies also indicated the rate of oral contraceptive use in IGM patients can reach up to 54.79%.[95] Additionally, the inhibitory effect of antipsychotic drugs on dopamine increases prolactin secretion of prolactin.[96] A study reported[97] that 19 cases of IGM were caused by long-term oral psychoactive drugs, and other studies have also suggested that hyperprolactinemia induced by psychoactive drugs is related to IGM.[98,99] Elevated prolactin levels are caused by disease and drug-related factors. Diseases include pituitary adenoma, craniopharyngioma, spontaneous elevation, and drug factors, including antidepressants and antipsychotics (Table 2). Therefore, imbalances in the secretion of estrogen, progestogen, or prolactin, either inherent or drug-induced, can alter the microenvironment of the mammary gland. This may induce immune and bacterial dysregulation, thereby promoting mammary duct injury and inflammation[100] (Table 1).

Diagnosis

Imaging diagnosis

Imaging examinations included breast ultrasound, mammography and breast magnetic resonance imaging. However, the imaging findings of IGM are highly similar to breast cancer, and it is often difficult to distinguish it from breast cancer.[102]

Breast ultrasound is cost-effective and convenient to perform, making it the preferred choice for imaging examinations. Under ultrasound, the IGM demonstrated solitary or multiple hypoechoic regions with irregular configurations and indistinct boundaries, which were tubular extensions or cavities containing foam debris and separation.[103–106] In advanced cases, due to the liquefaction of necrotic tissue, the echo patterns become diverse and may form abscess cavities or fistulas.[107,108] IGM is similar to breast cancer under ultrasound, but its diameter is often larger than that of breast cancer.[108,109]

Table 2 Risk Factors of Hyperdense Prolactinemia

Factors	Type	Number	Ref
Disease Factors	Pituitary adenoma	2	[89]
	Craniopharyngioma	1	
	Spontaneous elevation	1	
Drug Factors	Prednisolone, Azathioprine, alfacalcidol, Sulpiride	1	[93]
	Fluphenazine, Zolpidem, Duloxetine	1	
	Risperidone	1	[94]
	Flufenazine, Zolpidem, Duloxetine, Risperidone, Risperidone	6	[97]
	Risperidone+Clozapine	4	
	Aripiprazole+Fluvoxamine	2	
	Clozapine	1	
	Olanzapine	2	
	Olanzapine+ Ziprasidone+Quetiapine	2	
	Aripiprazole+Sulpiride	2	
	Risperidone	1	[101]

IGM can be manifested as single or multiple irregular masses with increased density and blurred boundaries in mammography, which is characterized by focal asymmetry.[103,110,111] Related clinical manifestations also include skin thickening and axillary lymph node enlargement.[103] Mammography is superior to breast ultrasound in the identification of calcification, but it is necessary to compress the breast during the examination to increase the pain of the affected breast. Patients may discontinue the examination due to severe pain. In the process of strong extrusion, it even increases the risk of inflammation diffusion.

Magnetic resonance imaging (MRI) can show the range of the mass and its relationship with the surrounding tissue more clearly. Heterogeneous enhancement mass or edge enhancement lesion is the most common imaging manifestation of IGM, which may also be accompanied by segmental or regional non-mass enhancement.[109–112] Imaging examination is often considered to lack specificity.[113] Finally, further pathological biopsy is needed to confirm the diagnosis.

Pathological Diagnosis

Pathological diagnosis is still the gold standard for the diagnosis of immune granuloma (IGM), which can make up for the deficiency of imaging examination. Correct pathological diagnosis depends on high-quality samples. Fine needle aspiration and biopsy needle aspiration are two commonly used pathological diagnosis methods. Studies have reported that the sensitivity of tissue samples for fine needle aspiration is 21.1%, and the sensitivity of tissue samples for biopsy needle aspiration is 96%.[114,115] The reason for the difference may be the difference in tissue volume.[114,115] Compared with fine needle aspiration, the samples obtained by biopsy needle puncture are more ideal in quality and quantity. In addition, the space between the inflammatory tissues can be opened while the biopsy needle is punctured, which promotes the discharge of pus.

Pathological features lobular-centered, non-necrotizing granulomas with multinucleated giant cells, epithelioid histiocytes, lymphocytes, plasma cells and neutrophils.[116] The parenchyma usually manifests as a loss of acinar structure and ductal injury.[63–65] Recent studies have also discovered a special pathological type characterized by a well-defined vacuole in the center of the granuloma surrounded by neutrophils. Corynebacterium can be seen under Gram stain, and IGMwith this pathological feature is thus named “cystic neutrophilic granulomatous mastitis”.[73] However, whether this form of IGM is a subtype of idiopathic granulomatous mastitis or a separate type of mastitis remains controversial.[117,118]

The pathological diagnosis of IGM should be distinguished from breast tuberculosis. Lacambra et alshowed that IGM is characterized by a significant increasein plasma cells, while tuberculosis changes are characterized by fibrosis, eosinophilia, and necrosis.[118]

Pathogen Detection

Current pathogen detection methods include traditional culturing, first-generationsequencing (Sanger sequencing), next-generation sequencing (NGS), and nanopore-targeted sequencing (NTS). Conventional culture method is commonly used to detect pathogenic bacteria in clinic. However, the positive detection rate remains low for unknown pathogens or those with highly stringent growth requirements. For example, Corynebacterium kroppenstedtii, which needs at least 72 hours ofculture time, grows poorly on ordinary medium,[67,119] but prolongs the culture time and grows well in the same medium supplemented with 1% Tween 80.[67,120,121]

NTS being the latest gene sequencing technology.[113,122] Compared to traditional next-generation sequencing, NTS has the advantages of ultra-long reads, high sensitivity/accuracy, simultaneous detection of DNA and RNA, and the ability to report within 24 h.[117] NTS is also capable of meeting rapid, comprehensive, and accurate clinical needs. Previous studies have shown that the early detection rates of nanopore-targeted sequencing are 91.7% and 94.4%, respectively.[20,118] In clinical settings, NTS is currently used to assist the diagnosis of endophthalmitis, respiratory tract infections, meningitis, among other diseases.[118] A recent study using NTS to detect pathogenic bacteria in IGM showed that this method achieves a higher bacterial detection rate than that of the culture method, with the dominant bacteria being Corynebacterium species (64%), especially Corynebacterium kroppenstedtii.[20]

Treatment

There is currently no standard treatment for IGM. Methods used in IGM treatment can be divided into conservative and surgical treatment categories. Conservative treatment options include hormone therapy, antibiotics, immunosuppressants. Surgical treatments included drainage and extended resection. Debate surrounds optimal treatment for IGM, including the appropriateness of conservative versus surgical approaches, treatment effects, and recurrence rates. An overview of treatment methods and outcomes is presented below.

Hormone Treatment

Drug therapy is the first choice for initial treatment of IGM, and a large number of reports have reported the use of hormones as the first-line treatment.[119] Hormone therapy includes administration of systemic oral hormones, local injections, and steroids. No standard procedure for the dosage and duration of treatment exists to date. A clinical trial[120] reported the oral administration of prednisone 32 mg (16 mg bid) daily, with the dose being tapered until the medication was stopped after 2 months. All patients were found to enter remission, and a recurrence rate of 11.9% was observed. Another clinical trial[121] reported that 20 mg of methylprednisolone was administered orally per day, and the dose was gradually reduced until the condition of the patients stabilized. A total of 80.7% of patients responded well to steroid therapy, and 33% experienced recurrence thereafter. However, the efficacy of glucocorticoids such as methylprednisolone varies between studies. This compound can completely revert the symptoms and prevent recurrence; however, it can also lead to poor treatment response. During treatment, a dose reduction can lead to disease progression or recurrence after the end of treatment. Several studies also showed that, upon reducing the dosage levels of hormones, an approximately 50% recurrence rate was obtained[123] (Table 3).

A previous study has compared the efficacy and recurrence rates of different doses. The remission rate with 5 mg of oral prednisolone daily was 53.3% and the recurrence rate was 37.5%. However, after oral prednisolone 50 mg on Day 1–3, 25 mg on Day 4–6, 12.5 mg on Day 7–9, and then maintained at 5 mg, the remission rate was 93.3% without recurrence.[124] However, another study found that higher doses were ineffective.[125] The study reported a 39.1% recurrence rate with a daily tapering from 100 mg to 5 mg, whereas 30 mg tapered daily to 5 mg with drainage had a recurrence rate of 19.1%. Therefore, the choice of dosage remains key to treatment. According to previous studies, patients treated with high doses have high remission and low recurrence rates. However, excessively high doses not only do not reduce the recurrence rate, but also increase the risk of recurrence and are likely to cause serious steroid-related complications such as Cushing's syndrome, weight gain, dyspepsia, hyperglycemia, hypertension, and blurred vision.[111,125,137] These complications lead to poor patient compliance and self-discontinuation of medications, resulting in treatment failure. However, extremely low doses have a poor remission effect and may lead to disease progression and recurrence.[124] Therefore, excessively high and low doses were not conducive to disease control (Table 3).

In addition to systemic oral steroid therapy, local steroid injections and topical hormone creams are also effective in IGM treatment. Local treatment with injectable steroids is based on the well-established injection-based procedure to treat diseases such as arthritis.[126] According to previous reports, local injection of 80–160 mg triamcinolone acetonide (40 mg/mL) achieved remission after an average of 2 months.[126] Another study reported that local injection of triamcinolone acetonide (20 mg/cm3) in addition to skin application of 0.1% triamcinolone acetonide cream resulted in a remission rate of 93.5% and a recurrence rate of 8.7% after three months.[24] Moreover, 0.125% prednisolone cream was applied topically twice daily until clinical remission, with a remission rate of 82.9% and a recurrence rate of 14.7%.[127] Nevertheless, local injection and skin application of steroids have certain side effects, mainly manifested as local skin thinning, dryness, local hematoma, skin telangiectasia, and secondary skin infection cellulitis.[24,127,138] Hence, compared to systemic treatment, local treatment can achieve higher effectiveness, with side effects mostly localized and lighter than those of systemic treatment and higher patient compliance (Table 3).

Antibiotic Therapy

Antibiotics are also commonly-used in IGM treatment, yet there are no standard procedures for medication and dosage adjustment. A total of 206 patients in Iran were treated with cloxacillin, cefalexin, ciprofloxacin, or clindamycin for 20

Table 3 Treatment of Idiopathic Granulomatous Mastitis

Treatment Method	Number	Medication	Remission	No Remission	Recurrence	No Recurrence	Side Effect	Ref
Bromocriptine+ drainage	3	NA	3	0	3	16	NA	[97]
Bromocriptine+ corticosteroid+ surgery	4	Methylprednisolone 20 mg/day	4	0			NA	
Bromocriptine+ corticosteroid	6	Methylprednisolone 20 mg/day	6	0			NA	
Bromocriptine+ glucocorticoids +antibacterials	3	Rifampicin 0.45g, Isoniazid 0.3g, Pyrazinamide 0.75g/day+Methylprednisolone 20mg/day	3	0			NA	
Bromocriptine+ surgery	2	NA	2	0			NA	
Bromocriptine+ corticosteroid+ antibacterials+ surgery	1	Rifampicin 0.45g, Isoniazid 0.3g, Pyrazinamide 0.75g/day+Methylprednisolone 20mg/day	1	0			NA	
Hormones+ antibiotics	21	Methylprednisolone 16mg, twice a day, dose reduced after 2 weeks for 2 months +unknown antibiotics	21	0	4	17	NA	[120]
Hormones	36	Methylprednisolone 16mg, twice a day, dose reduced after 2 weeks for 2 months	36	0	8	28	NA	
Hormones+ surgery	9	Methylprednisolone 16mg, twice a day, dose reduced after 2 weeks for 2 months	9	0	1	8	NA	
Hormones+ immunosuppressive drugs	2	Methylprednisolone 16mg, twice a day, dose reduced after 2 weeks for 2 months +Azathioprine	2	0	0	0	NA	
No treatment	50	NA	50	0	1	49	NA	
Hormones	72	Methylprednisolone 20g per day. After achieving complete remission (CR) or stable disease (SD), the dose of methylprednisolone reduced by 4mg every 2–4 weeks. During steroid treatment, patients undergo regular outpatient clinical visits every 2–4 weeks.	30	9	21	42	Cushing's syndrome+obesity	[121]
Low-dose hormones	15	5mg per day for two months	8	7	3	12	NA	[124]

(*Continued*)

https://doi.org/10.2147/IJWH.S536970

Table 3 (Continued).

Treatment Method	Number	Medication	Remission	No Remission	Recurrence	No Recurrence	Side Effect	Ref
High-dose hormones	15	50mg for 3 consecutive days, 25mg for 3 consecutive days, then 12.5mg for 3 consecutive days, followed by 5mg daily for 2 months.	14	1	0	0	NA	
Surgery	17	Surgical removal of inflamed breast tissue at healthy edges	NA	NA	7	10	NA	[125]
High-dose hormones	23	High-dose Prednisolone (50mg), twice a day for two consecutive weeks, gradually reduced to 50mg, 25mg, 10mg and 5mg per day according to the treatment response and clinical examination.	NA	NA	9	14	7 cases of hyperglycemia, 8 cases of headache, 6 cases of hair loss, 2 cases of mild blurred vision	
Low-dose hormones+ drainage	47	Steroids 30mg/day for 2 weeks, tapered to 20mg/day for 4 weeks, 10mg/day for 2 weeks, and then 5mg/day for 2 weeks.	NA	NA	9	38	4 cases of mild hypoglycemia, and 5 cases of gastrointestinal problems such as stomach pain.	
Observation	28		28	0	28	0	NA	[126]
Local injection	12	40 (Triamcinolone acetonide 40mg/mL), ranging from 2mL (80mg) to 4mL (160mg)	12	0	12	0	NA	
Surgery	9		9	0	9	0	NA	
Local injection of steroids+skin application of steroid cream	46	Triamcinolone acetonide (40mg/mL), 20mg/cm3, once a month+local administration of 0.1% triamcinolone acetonide, twice a day to treat the skin of breast lesions, every other day, for one month	37	9	4	42	1 case of local skin thinning	[24]
Oral hormones	32	Methylprednisolone 32mg/day for one month	23	9	15	17	3 cases of hirsutism, 1 case of weight gain	
Skin application of steroid cream	41	Prednisolone 0.125% cream, twice a day until complete remission	34	7	5	36	10 patients with local side effects, 1 patient with skin cellulitis, 9 patients with thinning/dry skin and telangiectasia, 1 patient with systemic side effects, and 1 patient with weight gain±hirsutism	[127]
Oral hormones	34	0.8 mg/kg once after meals	29	5	6	28	13 patients with systemic side effects, 11 patients with weight gain±hirsutism, and 2 patients with iatrogenic treatment	

Oral hormones +local skin application of hormone cream	33	Prednisolone 0.125% cream, twice a day	27	6	6	27	7 patients with local side effects, 2 patients with skin cellulitis, 5 patients with skin thinning/dryness and telangiectasia, 10 patients with systemic side effects, 9 patients with weight gain±hirsutism, 1 patient with iatrogenic treatment	
Antibiotics	19	Amoxicillin plus Clavulanic acid	29	NA	2	29	NA	[21]
	5	Sodium fusidate						
	1	Azithromycin						
	1	Ciprofloxacin+ Ornidazole						
	5	Others						
Antibiotics	30	Rifampicin at a dose of 300mg, twice a day	30	0	0	30	NA	[128]
Antibiotics	22	Doxycycline at a dose of 100 mg, twice a day	16	6	NA	NA	NA	[23]
Immunosuppressive drugs	60	Take methotrexate monotherapy 15mg/week for 24 consecutive weeks, and folate 10mg/week as a supplement for all patients.	52	8	52	8	NA	[129]
Immunosuppressive drugs+ hormones	41	The median dose of methotrexate is 15mg/week, respectively	41	0	NA	NA	Gastrointestinal symptoms	[18]
	3	Azathioprine 125 mg/day	2	1	NA	NA		
	3	Steroid hormone 40 mg/day	3	0	NA	NA		
Immunosuppressive drugs+ surgery	4	NA	4	0	NA	NA		
Immunosuppressive drugs	19	Methotrexate is administered at a dose of 10–15mg/week, increasing to 20–25mg/week per oral (PO) or subcutaneous (SC) based on clinical response.	12	5	3	14	Two cases (10.5%) of nausea, and one case (5.2%) of elevated liver function test	[130]
Immunosuppressive drugs+ hormones	17	Methotrexate 5mg/week+prednisone 8mg/day for 2–3 months	13	4	0	17	NA	[131]
Hormones +minimally invasive rotary resection	30	The initial dose of methylprednisolone is 20mg/day, reduced to 16, 12, 8 and 4mg/day every 1–2 weeks until discontinuation.	26	4	3	27	One case of postoperative bleeding	[132]
Vacuum sealing drainage (VSD)	30	NA	30	0	2	28	NA	[133]
Ultrasound-guided precise debridement	29	NA	29	0	2	27	NA	

(*Continued*)

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Table 3 (Continued).

Treatment Method	Number	Medication	Remission	No Remission	Recurrence	No Recurrence	Side Effect	Ref
Minimally invasive comprehensive treatment	69	Perform pus drainage, lesion resection and drainage tube placement after minimally invasive surgery, and iodophor, metronidazole, and dexamethasone are used to flush the lesion after the operation	69	0	7	0	NA	[134]
Wide resection+ skin flap transplantation technology	68	NA	68	0	3	65	NA	[25]
Surgery+Yanghe Decoction Scheme	28	Yanghe Decoction is a traditional Chinese medicine made from degelatined antler, licorice, cinnamon, processed ginger root, white mustard seeds, rehmannia glutinosa and ephedra herb (honey-fried).	27	1	NA	NA	NA	[135]
IEPED+surgery	60	IEPED is made from 12 grams of atractylodes macrocephala, 12 grams of pangolin, 12 grams of ginseng, 12 grams of angelica sinensis, 9 grams of cohosh, 9 grams of licorice, 15 grams of angelica sinensis, 15 grams of astragalus membranaceus, 10 grams of licorice, and 10 grams of dried green orange peel.	54	6	0	60	NA	[136]
Bromocriptine	1	Bromocriptine 2.5mL, twice a day	1	0	0	1	NA	[101]

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days. Only 6 (3%) patients entered remission.[139] In another study, 31 patients were treated with a combination of amoxicillin and clavulanic acid, sodium fusidate, azithromycin, and a combination of ciprofloxacin ornidazole, of which 29 achieved complete remission, and two patients experienced recurrence. The average remission time was 2.5 months.[21] In another study, 17 of 21 patients achieved complete remission after antibiotic treatment, four recurred in subsequent follow-up. No time of remission was not reported.[120] In an 11-year single-center study, only nine of 17 patients treated with antibiotics alone reported remission, with an addition four subsequently entering remission.[22] Antibiotic therapy thus remains controversial due to its variable therapeutic effects. The reasons behind this may include the complexity of pathogens, gradual resistance of pathogens to antibiotics, and the length of treatment time (Table 3).

Corynebacterium has been reported to show resistance to several drugs.[140] Corynebacterium is a lipophilic bacterium that relies on lipids for its growth and reproduction. The bacterium is resistant to hydrophilic antibiotics, such as B-type amide (penicillin) and quinolone penicillin (levofloxacin).[71,141] The resistance rate of IGM infected with Corynebacterium to penicillin can be as high as 70%.[22] Most Corynebacterium strains were found to be sensitive to rifampicin, co-trimoxazole, doxycycline, linezolid, and vancomycin.[1,13,140,142,143] In a study that used rifampicin as the first-line treatment, 18 and 12 out of 30 patients showed remission at 6 and 9 months, respectively. The median follow-up time was 15.5 months with no disease recurrence.[128] Another study used doxycycline as the first-line drug for IGM, and 50% of the patients achieved complete remission after treatment.[23] In general, Corynebacterium species were associated with a longer duration of treatment and a higher risk of recurrence.[22,144,145] Corynebacterium has been reported to require a shorter treatment duration in patients receiving anti-Corynebacterium therapy than in those who did not receive treatment.[144] Therefore, anti-Corynebacterial treatment is a key step that should not be ignored. Other studies have also shown that the recurrence rate of antibiotics plus hormone therapy is lower than that of hormone therapy alone, indicating that antibiotic therapy plays an important role in reducing the duration of treatment and recurrence rate[142] (Table 3).

Immunosuppressive Agent Therapy

The most commonly used immunosuppressive drug used in IGM treatment is methotrexate (MTX), followed by azathioprine.[18,146] The main mechanism of action of methotrexate is the inhibition of the transformation of folate into tetrahydrofolic acid, which participates in cell proliferation. Methotrexate also inhibit other folate-dependent enzymes and exert anti-inflammatory effects.[147] It is also used to treat psoriasis, rheumatoid arthritis, and other diseases.[147] However, methotrexate usage is less common than that of antibiotics or corticosteroids in IGM treatment, and is usually considered an alternative in case of cortisol resistance or recurrence.[148] The largest MTX monotherapy studies to date have shown that after 6 months of MTX treatment in 64 patients, 81.25% achieved complete remission.[129] In a study by Postolova et al,[130] patients for whom hormones, antibiotics, and surgery failed, were treated with methotrexate alone for a median treatment time of 15 months. A total of 75% of the patients achieved remission, 94% showed improvement, and 15.8% showed improvement after switching to subcutaneous administration (Table 3).

Immunosuppressive drug treatment combined with steroid hormones can achieve certain level of effectiveness with lower steroid hormone doses and less side effects. In such a study, 41, 3, 3, and 4 out of 51 patients received methotrexate, steroid hormones, azathioprine and steroid hormones, and only steroid hormones, respectively. Among them, 50 patients achieved complete or partial remission, and one patient developed thrombocytopenia and Sjögren's syndrome after using azathioprine. No recurrence was observed in any of the patients.[18] Another study reported that 80 patients who failed initial treatment with methylprednisolone were treated with methotrexate (7.5 mg/week) and low-dose methylprednisolone (4–8 mg/day). Among them, 44 patients achieved complete remission, 17 achieved partial remission, and subsequent surgical treatment achieved complete remission. Only five patients experienced mild hair loss, and no other side effects were observed.[148] In addition, 17 patients were treated with 5 mg/week methotrexate and 8 mg/day low-dose prednisone. After 3 months of treatment, 10 patients achieved complete remission, 3 achieved partial remission and subsequent complete remission after surgery, 4 showed no response to treatment, and no side effects occurred[131] (Table 3).

Surgical Treatment

Surgical treatment is an option for patients for whom conservative treatment fails, recurrence is observed within a short period, or for those who refuse treatment with steroid hormones. In patients with pus in the lesion, traditional incision and drainage, needle aspiration, or needle or catheter drainage can be performed. However, the use of drainage alone has been reported in only a few cases, which may explain the higher recurrence rates associated with traditional drainage.[21] Lesions that cannot be cured by drainage or appear as masses can be surgically removed. The surgical methods used for this purpose include minimally invasive rotary resection,[134] breast lesion resection,[149] extended lumpectomy,[149] lumpectomy plus skin flap transplantation,[25] and nipple-areola complex-sparing subcutaneous mastectomy and prosthesis implantation[150](Table 3).

Minimally invasive surgery is feasible when drug treatment results in no acute lesions or when the lesions shrink. In one study, the lesions of 30 patients were divided into four types under ultrasonography: 0 cases of diffuse type, 17 cases of patchy hypoechoic type, 9 cases of localized abscess type, and 4 cases of localized hypoechoic mass type. A minimally invasive rotary resection was performed after glucocorticoid treatment, which cured 26 patients (86.7%), whereas 1 patient had postoperative bleeding, and 3 patients had recurrence (10.00%). All 3 recurrent cases were hypoechoic.[132] In addition, another study reported that patients treated with vacuum sealing drainage (VSD) and ultrasound-guided precise debridement were cured, with an overall recurrence rate of 6.8%, an overall new incidence rate of 8.5%, and an average disease duration of 5.3 months.[133] Another study proposed a minimally-invasive comprehensive treatment. In this study, 69 patients underwent pus drainage, lesion resection, and drainage tube placement after minimally invasive surgery. Iodophor, metronidazole, and dexamethasone were used to flush the lesion after the operation. All patients were cured, and seven (10.17%) patients experienced recurrence after a year of follow-up[134] (Table 3).

If there are multiple fistulas and large ulcers on the surface of a patient's breast, skin flap transplantation technology can be used to repair the wound after wide resection. In such a surgical study, a random breast dermo-glandular flap (BDGF) was used to correct tissue defects, with only three patients experiencing recurrence after surgery (3/68, 4.4%).[25] For patients with large lesions that cannot be completely relieved or even progress with other treatments, to avoid scarring caused by multiple breast surgeries, subcutaneous mastectomy and prosthesis implantation can be performed to avoid scarring caused by multiple breast surgeries, and to obtain an aesthetic effect[150] (Table 3).

However, the effectiveness of the surgical treatment remains controversial. According to statistics, the recurrence rate after surgical treatment ranges between 5% and 50%,[3,151] and the highest reported incidence rate is 72.7%.[151] However, other studies reported that patients who do not respond to conservative treatment can achieve complete remission without recurrence after surgery.[139] A meta-analysis noted no significant difference in recurrence rates between patients treated nonoperatively and surgically.[152] In general, surgical treatment can save patients who fail to respond to conservative treatment to a certain extent, preventing further development of skin ulceration or even extensive necrosis. Early surgery can prevent unnecessary mastectomy as well (Table 3).

Traditional Chinese Medicine

Traditional Chinese medicine has a history of thousands of years. Traditional Chinese medicine aims to regulate the balance of Yin and Yang in the body through different combinations of animal and plant products as well as minerals to cure diseases. Traditional Chinese medicine has also been used to treat IGM. Chuang Ling Ye (CLY) is a traditional Chinese medicine compound composed of rhubarb, safflower, A. manihot, and T. chebula. A study included 40 patients who needed to change dressings. Twenty patients in the experimental group used 30 mL CLY local flushing when changing dressings, while the control group did not use CLY. After 4 weeks of follow-up, the range of inflammation in the experimental group was significantly smaller than that in the control group, and the difference was statistically significant.[153]

Yanghe decoction is another traditional Chinese medicine obtained from degelatine antler, licorice, cinnamon, processed ginger root, white mustard seeds, Rehmannia glutinosa, and ephedra herb (honey-fried). The results showed that Compared with patients who underwent surgery only, those who received adjuvant Yanghe decoction following surgery showed a shorter remission time with a higher rate (96.4% vs 76.0%) as well as a lower recurrence rate (0% vs 16.0%)[135] (Table 3).

Internal expulsion pus-expelling decoction (IEPED) was prepared from 12 g of Atractylodes macrocephala, 12 g of pangolin, 12 g of ginseng, 12 g of Angelica sinensis, 9 g of cohosh, 9 g of licorice, 15 g of Angelica sinensis, 15 g of

Astragalus membranaceus, 10 g of licorice, and 10 g of dried green orange peel. In several studies,[136] IEPED was soaked in sterile gauze, which was stuffed into the lesion after debridement. The total effective rate of the control group without IEPED was 68%, and the total effective rate of the experimental group with IEPED was 90%. During the 1-year follow-up, 1 patient in the control group relapsed, and there was no recurrence in the experimental group. In addition, it has been reported that traditional Chinese medicine combined with surgery leads to a higher recovery rate and shorter disease duration.[154] The efficacy of traditional Chinese medicine in IGM is thus promising (Table 3).

Targeted Prolactin-Lowering Therapy

Treatment of IGM caused by anti psychoactive drug-induced prolactin elevation has also been reported. In a study on mastitis caused by elevated prolactin levels induced by psychoactive drugs, anti psychoactive drugs were first reduced or replaced, and bromocriptine was used to reduce prolactin, followed by surgery, steroid hormones, and antibiotics. A total of 16 of 19 patients were completely cured, and 3 patients experienced recurrence.[96] Similar studies have suggested that a targeted reduction in prolactin levels could effectively control inflammation and avoid unnecessary surgery as well[101] (Table 3).

Observation

Several studies have suggested that IGM is a self-limiting disease, and mere monitoring of the patient is also a viable option for disease management.[8] This is based on the observation that 15.1% of patients achieve remission within nine months of diagnosis without any treatment.[155] Another report also stated that 42.4% of the patients recovered under monitoring without any treatment[120] (Table 3).

Recurrence Factor

Patients with idiopathic granulomatous mastitis are prone to recurrent attacks that pose a significant challenge to clinicians. Therefore, the recurrence rate should be reduced during the course of treatment. Univariate analysis of related studies showed that differences in body mass index (BMI) and follicle-stimulating hormone (FSH)/luteinizing hormone (LH) ratios were positively correlated with IGM recurrence. In particular, the difference in PRL levels before and after treatment is an independent risk factor for recurrence, and patients with higher PRL levels after treatment have a higher risk of recurrence[156] (Table 4). A Multivariate analysis identified low The serum albumin to globulin ratio and smoking as independent risk factors for IGM recurrence[157] (Table 4). Another Retrospective analysis revealed that patients with relapsing IGM exhibited high BI-RADS-defined background parenchymal enhancement (moderate to intense) and low mean apparent diffusion coefficient values (less than 1.00×10−3 mm2 /s) on MRI. The authors accordingly proposed that early-stage MRI evaluation should be considered, as high BPE and low mean ADC values might serve as potential markers for future recurrence.[158] A 2.16-fold to 2.64-fold increase in the recurrence rate of Corynebacterium infections has been reported[22,144,159] (Table 4). A systematic analysis explored the relationship between treatment methods and recurrence. Statistics found that the recurrence rate of the antibiotic treatment group was the lowest, and the difference was statistically significant.[160] Further studies are required to predict recurrence factors, and the risk of recurrence should be considered during the initial treatment to reduce the recurrence rate and avoid secondary lesions in patients.

Table 4 List of Recurrence Risk Factors

Factor	References
BMI≥24	[156]
Hyperprolactinemia	
Follicle-stimulating hormone (FSH)/luteinizing hormone (LH)	
Low The serum albumin to globulin ratio	[157]
Smoking	
Corynebacterium	[22,144,159]

Discussion

The etiology of IGM remains unclear, associated with many factors.[62,68,80,93,94] Whether IGM is an autoimmune disease or an infectious disease is controversial. Some authors believe that it is an autoimmune disease, because the study found that the immune indexes of IGM patients have different degrees of abnormalities, and methylprednisolone has a control effect on it. Another part of the authors believe that it is an infectious disease. Although pathogens are detected in IGM tissues, there is no conclusive evidence that the detected pathogens are pathogenic bacteria or colonized bacteria. Literature suggests that the occurrence and development of IGM is not determined by a single factor but rather by a combination of multiple factors, including hormone imbalance, flora disorder, and immune imbalance.[68,76,86]

Based on the existing literature, we believe that IGM is a damage response induced by the imbalance between the immune system and pathogens. In the microenvironment of the mammary ducts and acini, immune cells and pathogenic bacteria in mammary ducts and acini are in a dynamic balance (Figure 3A). However, changes such as hormone imbalance, increased endotoxins, cytokines, and complements released by the body,[161] disrupts the local microenvironment.[37] Alternatively, local breast impact injury and the increase in the type or number of local pathogenic bacteria may also disrupt the balance between the immune system and pathogens in the mammary ducts and acini[162] (Figure 3B).

Once imbalance occurs, immune cells attack the exposed pathogen. On one hand, due to the non-specific killing of some immune cells, and the pathogens are mostly located in epithelial cells, the immune cells directly damage the mammary epithelial cells in the process of killing pathogens. On the other hand, due to the release of granzymes, perforin, and other substances by activated immune cells, mammary epithelial cells are indirectly injured.[163–165] The destruction of mammary epithelial cells indirectly leads to pathogen invasion, which further activates the immune system. This cycle aggravates local inflammation, and expands the scope of the lesions (Figure 3C). To prevent expansion of the lesion, the body forms granulomas in the early stages of the lesion to prevent the development of pathogens (Figure 3D), which clinically manifest as a painful mass. As the disease progresses, immune cells kill pathogens, breast tissue increases, and a cavity with a large amount of pus is formed locally in the breast. If the process continues and the scope of the lesions gradually expands, breast sinus tracts and even breast skin ulcers form (Figure 3E).

The validity of this reasoning can be substantiated by multiple perspectives. Based on the pathology of the IGM lesions, granulomas are nodular foci formed by the proliferation of local inflammatory macrophages and their derivative cells. This is a special type of chronic inflammation[166,167] accompanied by delayed-type hypersensitivity during the entire process.[168]

Pathological results of IGM reveal not only a large amount of immune cell infiltration in the lesion[114] but also neutrophils surrounding Corynebacterium and other pathogens in the granuloma vacuoles,[72] in line with the characteristics of chronic inflammation.

From the perspective of pathogens, pus cavities and large amounts of pus can form in the IGM lesions. Various genera of pathogens and viruses have been identified in the IGM tissues and pus.[166,167] These studies have shown that pathogenic infections may be an important initiating factor for IGM,[20] especially Corynebacterium. A study infected rat models with Corynebacterium bacteria isolated from patient tissues. Researchers observed typical IGM pathological features in the mammary tissue of infected rats, as well as upregulation of the inflammatory factor IL-6 in rat blood and upregulation of IL-6 and TNF-αin mammary tissue.[169] The research team speculated that Corynebacterium is attracted by fatty acids in the breast to colonize in the breast, and secretes Corynekropbactin during colonization, which may play a role in chelating iron, destroying breast cells, inhibiting the growth of other colonized bacteria, and causing the up-regulation of inflammatory factor IL-6, which in turn leads to the formation and development of IGM.[169] Our speculation is consistent with this study, that is, external factors break the balance between pathogens and the immune system in the breast, causing the immune system to attack pathogens, thereby forming an immune injury response characterized by granuloma, in which Corynebacterium may be the main driver of this cascade.

In addition, the increase in white blood cells and CRP levels in blood indicators also proves the existence of a pathogenic infection.[48] Not all patients have standardized clinical manifestations and indicator changes; however, most patients undergo changes at a certain stage.

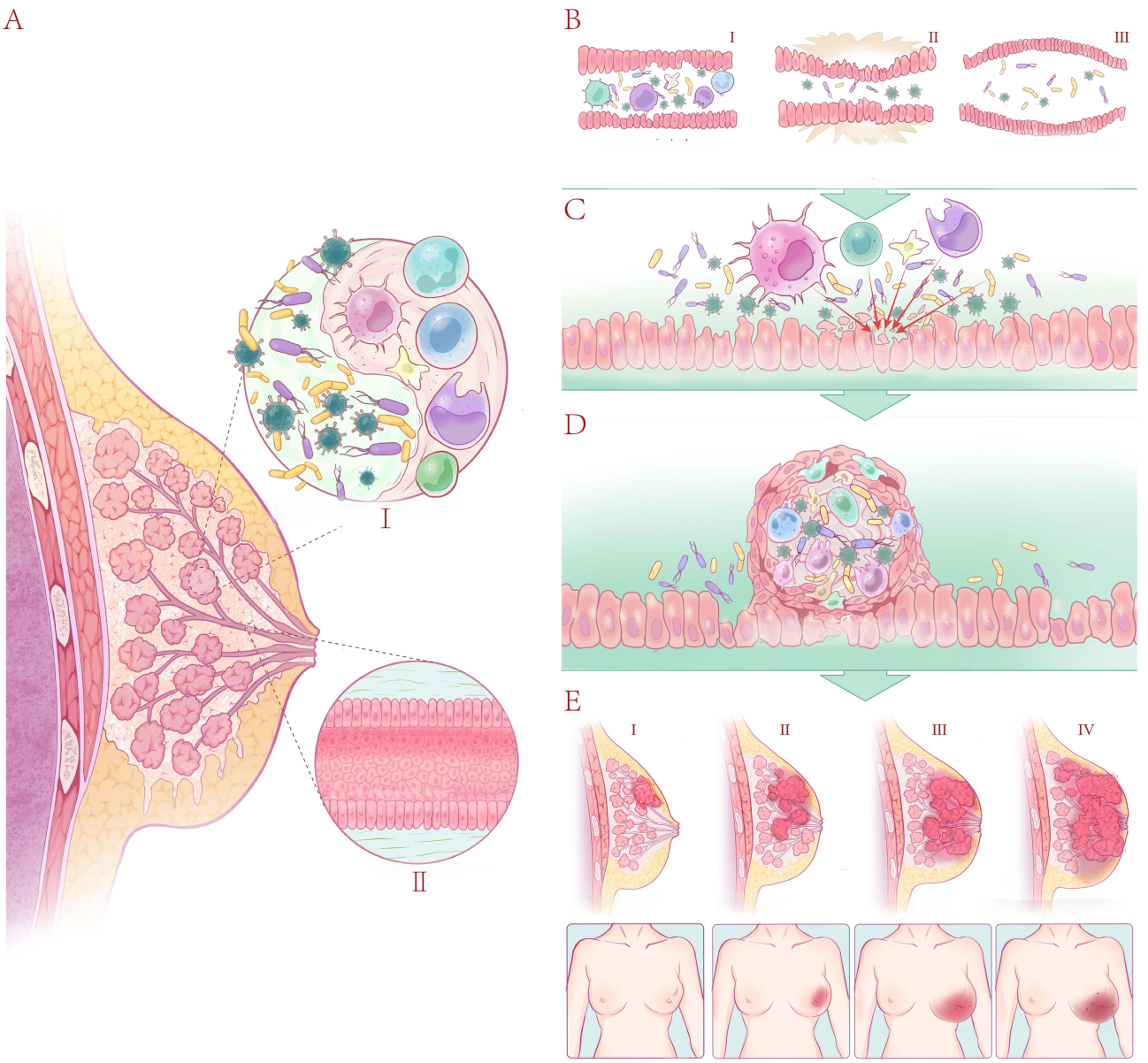

Figure 3 The "immunity-pathogen imbalance pathogenesis" model. (**A**) (I) In normal breast, the immune system is in balance with pathogens, and (II) the ductal epithelium is lined up. (**B**) (I) immune system imbalance, abnormal recognition ability enhancement. (II) breast impact injury directly leads to breast duct injury and exposes pathogens (III) hormone imbalance causes breast duct deformation to expose pathogens. (**C**) The above reasons lead to imbalance between pathogens and the immune system, immune cells attack exposed pathogens. (**D**) Long-term chronic inflammatory stimulation leads to granuloma formation. (**E**) (I) painful mass formation (II) galactapostema (III) breast sinus. (IV) breast ulceration with pus outflow. The C arrow in the figure shows that the immune cells attack the pathogens.

During immune regulation in IGM, the cell types and cytokines whose expression changes include NK cells, macrophages, T cells, B cells, CD4+ cells, CD8+ cells,[29,32] IL-23, IL-22, IL-6, IL-33, IL-17, IL-8, IL-10.[47–50] After recognizing pathogens, macrophages induce Th0 cells to differentiate into Th1, Th2, Th17, and Treg cells by producing cytokines, presenting antigens, and expressing co-stimulatory molecule.[170–172] NK cells release INF-y after activation, and DC release IL-12 and IL-23 after activation. IL-12 and INF-y act together on TH1 cells to activate TH1 cells,[173,174] and activated Th1 cells promote the macrophage secretion of INF-α, and INF-αpromotes macrophages to become epithelioid cells and form granulomas.[175] IL-12 promotes the release of IL-17, IL-6, IL-8, G-CSF, IL-17, IL-6, and IL-8 from CD4+T cells, whereas G-CSF promotes the activation of neutrophils, B lymphocytes, and Th0 cells. Tregs release IL-10 to inhibit TH1 cells, thereby suppressing the inflammatory response.[176] TH17 cells release IL-21 and IL-22; IL-22 inhibits the production of Th2 cells, and IL-12 combines with IL-17 to form antimicrobial peptides.[177,178] Th2

https://doi.org/10.2147/IJWH.S536970

cells release IL-4 to promote neutrophil and B lymphocytes.[179–181] During activation, CD8+ T cells release granzymes, perforin, and express FasL, resulting in epithelial cell injury[182,183] (Figure 4).

Currently, no standardized treatment protocols are available for IGM. Methods using hormone therapy, antibiotics, surgery, immunosuppressive drugs, probiotics, and traditional Chinese medicine have been reported. However, the absence of a standard treatment protocols lead to application of different treatment strategies by doctors with different levels of experience or using the same strategy for all patients. Hormone therapy is the first-line treatment used by most clinicians.[119]

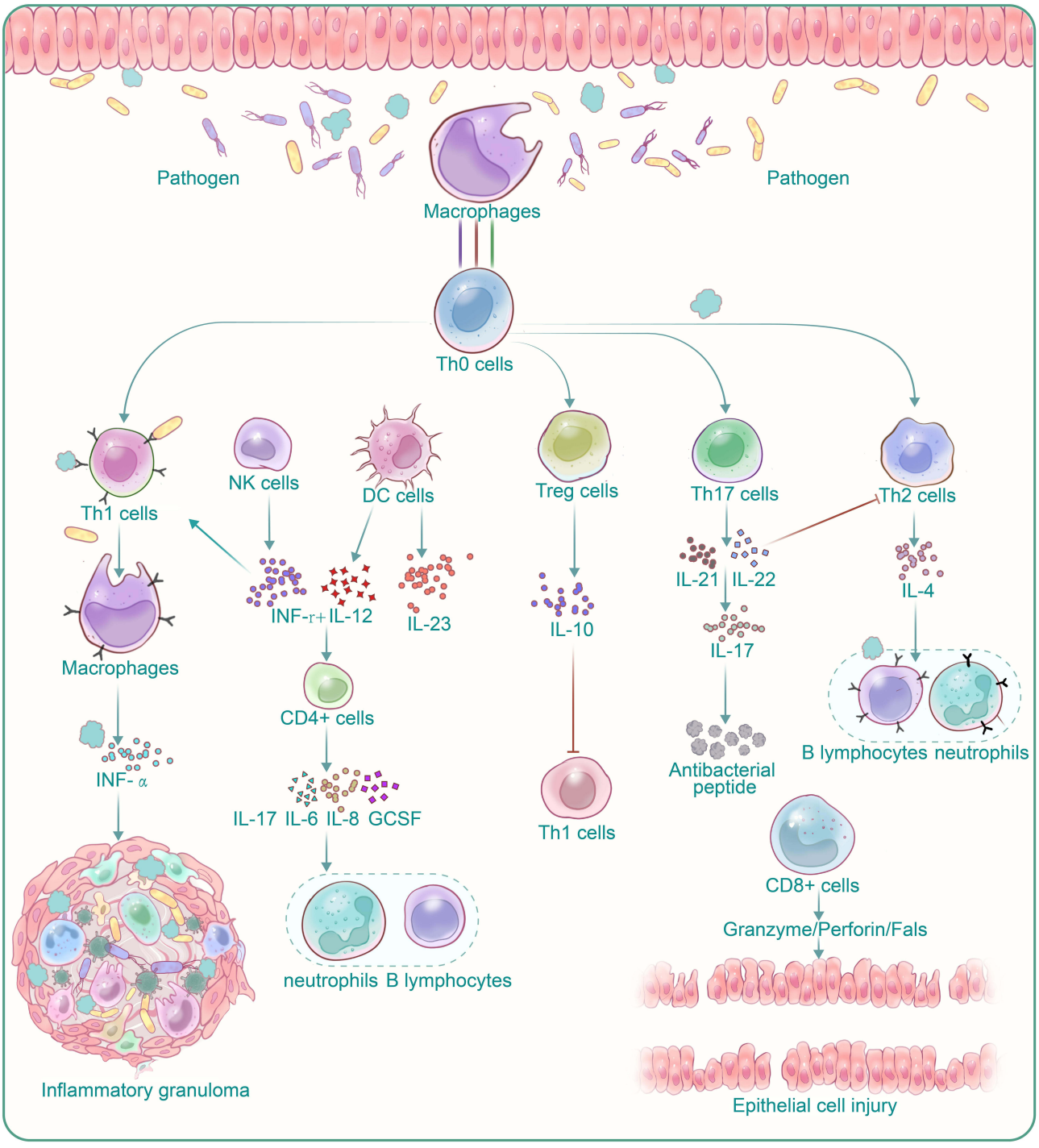

Figure 4 Immune mechanism of granulomatous mastitis.

Studies have shown that hormone therapy is indeed effective for IGM; however, the hormone dosage that maximizes the benefits and minimizes the side effects is still not clear, and some patients may still experience recurrence after hormone dose reduction or discontinuation.[123]

There are differences in the therapeutic effect of antibiotics, which may be related to the following factors: blind use of antibiotics without pathogen identification; there may be a mixture of multiple bacteria, and a single antibiotic or empirical antibiotic cannot cover all bacterial flora;[19] The presence of drug-resistant bacteria or bacterial resistance to empirical antibiotics may also lead to ineffective antibiotic treatment.[184,185] The identification of pathogens and the selection of antibiotics are difficult problems in treatment. In the past, due to the difficulty of pathogen identification, the results of pathogen culture were mostly negative in many cases, thus ignoring the use of antibiotics or blindly using antibiotics.

Long-term benefits of antibiotic therapy.[144] Therefore, the use of antimicrobial agents should be done before the pathogen detection, targeted drug strategy, to avoid the use of empirical antibiotics and frequent replacement of antibiotic regimens.[162,185,186] The sequencing method is preferred for the identification method, and the culture conditions conducive to the growth of Corynebacterium should be provided when using the culture method. After obtaining clear pathogen detection results, sensitive antibiotics were selected according to drug sensitivity. At present, the difficulty is the treatment of Corynebacterium krusei. It is reported that Corynebacterium is sensitive to rifampicin and gentamicin. Rifampicin shows good therapeutic effect and safety in the treatment of IGM, and rifampicin can be given priority.[187]

Immunosuppressive agents are often used as an alternative to hormone therapy. Although they are effective, they cannot be used as a first-line regimen. Methotrexate is a folic acid reductase inhibitor, which has dual effects of anti-tumor and immune regulation. It is mainly used in anti-tumor therapy and immunotherapy.[188] From the curative effect analysis, glucocorticoids can more quickly and effectively control the inflammatory response and relieve acute symptoms, while methotrexate has a slower onset and is not suitable for acute patients who need to quickly control symptoms. From the safety analysis, the side effects of methotrexate mainly include bone marrow suppression, liver function injury, renal function injury, gastrointestinal discomfort, fatal skin diseases.[189,190] Compared with the side effects of steroid hormones, such as edema, weight gain, hair removal, osteoporosis. The side effects of methotrexate are more serious. In contrast, in the case of obtaining the same therapeutic effect, the smaller the side effect, the greater the patient ‘s benefit. There is currently no evidence of methotrexate as a first-line treatment drug. In clinical practice, methotrexate is rarely used as a first-line drug. Further clinical trials are expected to evaluate the efficacy of methotrexate in the future.

The goal of IGM treatment is to improve the recovery rate and reduce recurrence. Studies have found that BMI, hormonal imbalance, and Corynebacterium infection are important factors that lead to an increased recurrence rate.[22,144] This highlights that mastitis cannot be treated using a single method, and individualized comprehensive treatment options should be adopted for different patients. Therefore, a comprehensive assessment should be made before deciding on treatment, strategy by considering possible systemic and local factors, such as the immune system, lesion condition (size, location, and presence of pus), pathogen detection results, sex hormone and prolactin levels, and the presence of oral contraceptives or psychoactive drugs. Only by considering all possible recurrence factors through comprehensive treatment can a good outcome and prognosis be obtained with fewer recurrences. It is expected that with the deepening of research, the etiology of IGM can be clarified, and effective and standardized treatment methods can be found.

Conclusion

Idiopathic granulomatous mastitis is an immune injury reaction caused by the imbalance between pathogenic bacteria and immune system under the action of multiple factors. Corynebacterium may be the initiating factor of immune cascade reaction.

Funding

This work was supported by the National Natural Science Foundation of China (82360557, 82260537) and the Biomedical Project of the Major Science and Technology Program of Yunnan Province (202302AA310046).

Disclosure

Siyi Wang and Rui Liu are co-first authors for this study. The authors report no conflicts of interest in this work.

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