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INVITED REVIEW – OPEN ACCESS

An Update on Granulomatous Lobular Mastitis: It is Time to Tell the Untold

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ABSTRACT

Objective: Granulomatous mastitis is an infrequent, benign, inflammatory disease of the breast that mostly affects young women of reproductive age. The main objective of this review was to clarify the latest terminology and to provide an update on the diagnosis and management.

Materials and Methods: A total of 792 granulomatous mastitis-related articles published in the English literature from 1965 to 2022 were reviewed.

Results: The management of this benign but daunting condition remains controversial, and there is no worldwide consensus regarding the best systematic treatment protocol. Good judgment is required to ensure optimal diagnosis and treatment.

Conclusion: This narrative review deals with the latest developments in the diagnosis, etiopathogenesis, and modern treatment of the disease.

Keywords: Mastitis, autoimmunity, granuloma, breast, lobular, sustainability

INTRODUCTION

Terminology and Definition

Idiopathic granulomatous mastitis (IGM), more commonly known as granulomatous lobular mastitis (GLM), is a rare, benign, chronic inflammatory breast disorder of unknown etiology (1–5). It was first described by Yuan et al. in 1970 and then by Kessler and Wolloch (1–3) in 1972. Recent developments regarding the etiology and nature of the condition have led to some confusion among clinicians. GLM has been classified into primary GLM or IGM, which is diagnosed by histopathology without an underlying source, and secondary GLM, which includes infectious and non-infectious origins (1, 3–5). This review aimed to clarify the latest terminology related to the condition and to provide an update on key issues related to diagnosis and management.

A PubMed search was conducted for granulomatous mastitis-related articles published in English literature. With the use of the search term {(Granulomatous Mastitis) OR (Granulomatous Lobular Mastitis)) OR (idiopathic Granulomatous Mastitis)}, a total of 792 articles were identified from 1965 to July 2022. A relatively new approach was adopted in this review to synthesize the evidence on research methods and relevant guidance for the management of patients with GLM.

Prevalence

Being a rare disease, most of the articles published on GLM consist of case reports or case series, and the true incidence and prevalence of the disorder have not been established for Türkiye or Europe (5, 6). However, the annual prevalence reported in the US between 2006 and 2008 was an average of 2.4 per 100,000 women between the ages of 20 and 40, and surprisingly, it was 12 times more common among Hispanic women (7). On the basis of the published case series, it is believed that GLM is more common in patients of Hispanic, Native American, Middle Eastern, and African descent, although no ethnic studies have been specifically conducted (6–9).

Etiology

Although a specific etiology of GLM has not been identified, hormonal disorders, autoimmunity, and microbiological agents are the three main hypotheses that have been adopted to explain the disease's origin (3). Recent studies conducted over the last 10 years have emphasized that other factors such as genetic factors, smoking, and alpha-1 antitrypsin deficiency may have a role in the pathogenesis of the disease. It remains unclear whether GLM is caused by a single factor or a combination of factors (5, 10–21). Autoimmunity is considered the strongest theory in explaining the cause. A "secretion hypothesis" stipulates those patients' secretions such as retained milk may stimulate both humoral and cell-mediated immunity (10, 11). We should not forget that if many factors are held responsible for the etiology of a disease or if many hypotheses are put forward, we probably know very little regarding the etiology of that disease.

Hormonal Disorders

Pregnancy, Delivery, and Breastfeeding

GLM mostly affects women of childbearing age (under the age of 50), especially those who have recently given birth or are breastfeeding, and there are very rare reports of affected men (1, 3–5). It is widely believed that hormonal changes, secretion, and inflammation occurring during pregnancy, delivery, and breastfeeding contribute to the pathophysiology of the disease, and this could explain why the condition is more prevalent between the ages of 20 and 40 when most pregnancies occur. However, several reports of male cases and a wide age range in women (11–83 years) make it difficult to attribute sole responsibility to pregnancy, delivery, and breastfeeding (3, 5, 9–14).

Oral Contraceptives (OCS)

The hormonal (secretion) hypothesis suggests that oral contraceptives (OCS) could be a potential etiological factor for GLM as they are known to increase breast secretion and affect breast glandular function (10, 15). Although OCS use has been reported in 0%–42% of patients with GLM, a direct causative link between OCS and GLM has yet to be established (10, 16, 17).

Hyperprolactinemia

Several retrospective studies and small case series have reported on GLM that is not associated with either pregnancy or delivery, and the development of the condition has been attributed to an increase in serum prolactin, hypersensitivity to circulating prolactin, and upregulation of prolactin receptors (1, 3–5). In a case series of 24 patients, seven of whom underwent assays for prolactin; Bani-Hani et al. (18) reported elevated prolactin levels in one patient (4.1%). In another report on 18 women, out of three patients (16%) who had recurrent GLM, two were found to have hyperprolactinemia (19). Neither report provided a clear explanation regarding a physiopathological mechanism that directly links prolactin levels with GLM. There have been some reports of patients developing GLM while on selective serotonin reuptake inhibitors (SSRIs), which are a known cause of hyperprolactinemia, but there is no clear evidence supporting SSRIs as a significant risk factor for GLM (20–23).

Autoimmunity

Although autoimmunity is the most popular and most concentrated etiological factor, the underlying pathophysiological mechanisms are not yet understood. The idea of an immunological basis for GLM has gained traction particularly because most cases of GLM demonstrate a good response to steroids and other immunosuppressive agents, even in cases with recurrence after surgery, suggesting that autoimmunity may have a role in the etiology of the condition (10, 19, 24, 25). Furthermore, several studies have reported on extramammary involvement in GLM patients, such as erythema nodosum (EN) or arthritis, which supports the autoimmunity hypothesis, along with the immunohistochemical confirmation of T-lymphocyte predominance (3, 19, 25). In some studies, inflammatory markers such as white blood cell count, erythrocyte sedimentation rate, and C-reactive protein serum level were found to be significantly higher in GLM patients with EN, and a more aggressive disease behavior was noticed in these patients (26, 27).

Autoantibodies and Rheumatoid Factors

There is a wide belief that autoantibodies may play a role in the etiopathogenesis of GLM, and there has been increased interest in such research, particularly in the last five years (28). As it is known, antibodies targeting normal protein structures located in the nucleus of any cell are called antinuclear antibodies (ANA). It is also well known that under normal conditions, antigens of nuclear origin such as dsDNA are not accessible to the human immune system as they are confined to the nucleus and mitochondria and are rapidly degraded by DNases located in the cytoplasm and endosomes. However, there is an exception to this; the aforementioned nuclear formations are sensitive to ultraviolet light, infection, drugs, etc. If these structures are exposed to the aforementioned external effects, they can be released from apoptotic cells. Anti-double-stranded DNA (anti-dsDNA) antibodies consist of a group of antinuclear antibodies (ANA) whose target antigen is double-stranded DNA. Although rheumatoid factor, ANA, and anti-dsDNA have been detected in some patients with GLM, autoantibody positivity's diagnostic and predictive significance has not been established (29).

T and B Lymphocytes

The main subgroups of lymphocytes in the human immune system are T cells, B cells, and natural killer cells. T and B lymphocytes are the only cells in organisms that can recognize and specifically respond to each antigenic epitope. Humoral immunity originates from B Cells, and cell immunity is dependent on T Cells. Helper T cells are a type of T cell that plays a critical role in the adaptive immune system. The adaptive immune system is also known as the acquired immune system. There must be an absolute balance between lymphocyte subsets for humans to establish and maintain a normal immune response. In a study by Erhan et al. (19) where T and B lymphocyte markers were examined in biopsy samples from GLM patients, researchers observed a predominance of T lymphocytes in the tissue samples. Emsen et al. (30) reported that in their cases with GLM, the absolute levels of cytotoxic T lymphocyte and natural killer cells were higher than those in the control group. Additionally, FOXP3, a well-known immune marker of T regulatory cells (Treg), has been shown to play an important role in the development of autoimmunity (31), and significant changes in FOXP3 expression and Treg subsets have been reported in a recent study by Ucaryilmaz et al. (32) on patients with active GLM lesion and during remission. The results of the studies mentioned above point to an imbalance in the immune system in IGM patients.

Proinflammatory Cytokines and Interleukins

Interleukins (ILs) are a type of cytokine that was previously thought to be produced only by leukocytes but was later discovered to be produced by many other body cells. ILs is mainly involved in the activation and differentiation of human immune cells. In addition to these duties, it has very important roles in the critical processes of the aforementioned cells, such as proliferation, migration, maturation, and adhesion. Interleukins are a large family of 18 specific molecules (IL-1 to IL-8). In a recent study, Koksal et al. (33) compared the serum levels of IL-4, IL-8, IL-10, IL-17, and TNF-alpha measured by human enzyme-linked immunosorbent assay in 47 patients with biopsy-proven GLM and 30 healthy women. IL-8 and IL-17 are alone implicated in the formation and chronicization of many inflammato-

ry diseases, including inflammatory arthritis. Researchers concluded that proinflammatory cytokines, including IL-8 and IL-17, may play a role in the pathogenesis of GLM but also noted that elevated levels of IL-10, particularly in patients during remission, were associated with better control of GLM by inhibiting the release of proinflammatory cytokines while also suppressing their function and activation. Although considered a local disease by most clinicians, cytokine changes in GLM indicate the possible involvement of a systemic immune disorder. This is supported by the results of another study, in which there were significantly higher levels of serum IL-22 and IL-23 titers in patients with GLM compared to healthy controls (34).

Human Leukocyte Antigens Class I and II

A special structure called human leukocyte antigens (HLAs) is produced specifically on all types of cell surfaces and regulates the immune response in a balance. Many studies have been conducted so far to reveal the relationships between various HLA types and various diseases. Recently, Koksal H determined the distribution of human leukocyte antigens (HLA) in 48 patients with biopsy-confirmed GLM and 50 healthy donors, where they found a significantly higher prevalence of HLA-A*10, HLA-A*2403, HLA-B*18, and HLA-DR*17 in GLM patients (35). An additional comparison of relapsers and nonrelapsers showed that those with HLA-A*3 and HLA-A*32 were more likely to have relapsed. The authors cited the significance of the study findings in helping in elucidating the etiopathogenesis of GLM (35).

Microbiological Agents

Several microbiological agents have been implicated in the etiology. The main agents implicated are the dominant microorganisms of the normal endogenous bacterial flora, which is very similar to the skin flora. These are coagulase-negative streptococci, Propionibacterium sp., and Corynebacterium sp., which are known to penetrate deeper into the breast tissue through the ductal system (3, 5, 10, 36). Taylor et al. (37) reported on GLM cases of tuberculosis in developing countries. Other unusual pathogens such as C. kroppenstedtii, P. oleovorans, human gammaherpesvirus, A. baumannii, and T. thermophilus have also been shown to be significant pathogenic factors for GLM. In a study by Bi et al. (4), using metagenomic next-generation sequencing, researchers identified the human gammaherpesvirus (Epstein–Barr virus) as a novel cause of mastitis. They also noted that abnormalities in sex hormone levels, as well as autoimmune dysfunction, were common in GLM patients and concluded that lipophilic antibiotics such as rifampicin and prolactin inhibitors may be effective in the treatment of GLM (1, 4).

Presenting Symptoms

Most patients with GLM present with a palpable breast mass, with lesions usually extending from the periphery of the breast to the areola (1, 10). Although this mass predominates with pain in some patients, it may be associated with widespread or localized redness of the breast skin, fistula formation with skin ulcerations, nipple retraction, abscess, and ipsilateral axillary lymph node enlargement in a substantial group of patients (3, 5, 38, 39). In some patients, mild tenderness due to focal mastitis may precede the development of a mass by 1 to 3 months, and fever as a systemic response is a rare finding (1, 10). Occasionally, a breast abscess may be the presenting complaint, and some chronic breast abscesses may develop into fistulas as the disease progresses (5, 10, 24, 38, 39).

Extramammary Symptoms

As previously mentioned, extramammary manifestations of GLM include EN, arthralgia, and episcleritis (5, 40). Arthralgia occurs more frequently in GLM patients with EN, which is also associated with higher rates of fistula development and recurrence (28, 29). Systemic involvement in the form of EN of oligo-/polyarthritis may appear later, and its presence supports a diagnosis of IGM (1, 3, 28).

Localization

GLM may involve a single breast or both breasts synchronously, although bilateral involvement is rarer, occurring in only 1% of cases (9) in one study. In another case series of 62 patients, Dalbaşı et al. (41) reported that 30 (48.38%) patients had lesions only in the right breast, 26 (41.94%) patients had lesions only in the left breast, and 6 (9.68%) patients had lesions in both breasts.

Seasonal Relationship

A seasonal variation with GLM has been touted by some experts. A retrospective analysis of data from 37 women with GLM between 25 and 49 years of age showed that between January 2015 and January 2020, all cases were diagnosed between September and May, with no statistically significant difference between the months or seasons (42).

Clinical Classification

The clinical presentations of cases vary widely from a small breast mass to complex multiple fistulas as this poses problems in comparing treatment outcomes and defining the severity of the disease. Irkorucu (43, 44) proposed a clinical classification system for standardization and accurate comparison of treatment modalities. According to the author, the disease is classified into six different types, summarized in Table 1.

Differential Diagnosis

GLM shares clinical features with several conditions, the most important of which being breast cancer should always be considered foremost in the differential diagnosis. GLM remains a diagnosis of exclusion - several other conditions such as tuberculosis; sarcoidosis; autoimmune conditions like Behçet's disease, Crohn's disease, Sjögren's syndrome, and systemic lupus erythematosus with granulomatosis and polyangiitis; diabetic mastopathy; and mammary duct ectasia may have similar presentations (5, 10, 14, 39, 45).

The next section of the differential diagnosis part will focus on tuberculosis mastitis (TM), the duct ectasia/periductal mastitis complex, and immunoglobulin IgG4-associated sclerosing disease, and each topic will be discussed separately.

Tuberculous Mastitis

The clinical presentation of TM is similar to GLM in that it may manifest as a breast mass or an abscess with drainage of the sinuses. Surprisingly, some patients with TM do not develop constitutional symptoms like fever and weight loss, which could make diagnosis challenging. Even aspiration cytology, tuberculin test, and histopathological examination of the lesion may not produce a positive result confirming a diagnosis. Making sophisticated tests such as polymerase chain reaction and molecular detection techniques are more reliable (1, 5, 16). The main pathological feature

Table 1. Irkorucu classification for GLM (44)

Type	Description
1	Limited superficial mastitis without abscess
2	Mastitis with abscess only
3	Mastitis with skin ulcer and fistula
4	Painful mass in one or both breasts, skin ulceration, complex mastitis with abscess and fistula
5	Recurrent disease
6	Mastitis with secondary complications of tuberculosis, sarcoidosis, syphilis, foreign body clearance, vasculitis, and fungal and parasitic infections

GLM: Granulomatous lobular mastitis

that could distinguish TM from GLM is the presence of caseation necrosis, which has been reported in 90% of cases with TM, compared to 10% of patients with GLM (17, 21).

The Duct Ectasia/Periductal Mastitis (DE/PDM) Complex

DE/PDM is extra-postpartum mastitis that mainly affects the mammary ducts, the pathogenesis of which remains unknown. Few studies have reported an association with stimulation of squamous epithelial cornification, infections, and smoking (10). The clinical manifestation and imagining findings of DE/PDM are very similar to those of GLM. However, nipple discharge and nipple retraction are usually more common in patients with DE/PDM, and breast masses are often observed below the areola, features that could help in distinguishing it from GLM (1, 3, 5, 21).

Immunoglobulin G4 (IgG4)-Associated Sclerosing Disease

The IgG4-associated sclerosing disease is a recently described clinicopathological entity that has been observed in several organs of patients with autoimmune pancreatitis (AIP). This systemic condition is characterized by the presence of tissue infiltration with T-lymphocytes and diffuse IgG4-positive plasma cells in various organs (46). The IgG4-associated sclerosing disease of the breast was first described in Japan in a patient with initial histopathological immunological findings very similar to GLM who responded to steroid therapy (21, 46). Researchers have suggested that this condition should be considered another extra-pancreatic manifestation of AIP.

Diagnosis

Detailed history and careful physical examination of clinical manifestations are required for a correct diagnosis of GLM, complemented by imaging, laboratory, and histopathology findings (1, 3, 5, 10).

Histopathology

As mentioned previously, GLM is a diagnosis of exclusion, and the first step should always be to exclude a breast malignancy clinically and histopathologically (3, 5, 10). GLM is characterized by the presence of noncaseating granulomas concentrated in the breast lobules, with an inflammatory background with a predominance of lymphoplasmacytic cells. Granulomas have typical features such as the presence of large numbers of Langhans giant cells, neutrophil polymorphs, and epithelioid histiocytes (Fig. 1). Additionally, findings on microscopical examination may include microabscesses, necrosis, sinus tracts, and canal ectasia, particularly in advanced cases (2–5, 39). Most tissue samples of GLM cases stain negative with gram stain, and tissue cultures are often negative (3, 5, 10, 39).

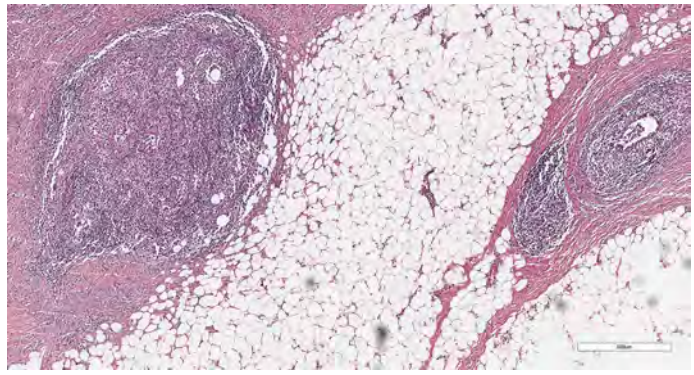

Figure 1. Lobulocentric granulomatous inflammation with multinuclear giant cells, dense lymphocytes, few plasma cells, and eosinophil leukocytes are observed in the sections. Duct structures can be seen in between granulomatous inflammation (H&E 40×)

Core needle biopsy of the lesion remains the undisputed gold standard for the diagnosis of GLM that is universally accepted by breast surgeons, with a reported sensitivity of up to 96% (3, 5, 47). In a Tru-cut biopsy, adequate material should be obtained. The pathologist and surgeon should not have any doubts regarding the diagnosis. If necessary, the biopsy should be repeated. The main challenge for histopathologists and clinicians is to distinguish GLM from other autoimmune and granulomatous diseases (5, 47, 48). Radiological findings of GLM on mammography or ultrasound are nonspecific and are often misinterpreted as they may mimic breast carcinoma. Therefore, histopathological confirmation is paramount before a decision regarding surgical intervention is made (5, 47, 48). Optimal diagnosis and management of GLM require a coordinated effort by a multidisciplinary team, including surgeons, pathologists, and radiologists, with a discussion on the ideal biopsy procedure and specialized histopathology stains (3, 5, 10, 46, 47).

Laboratory Findings

Routine investigations in patients with suspected GLM are recommended to include complete blood count, erythrocyte sedimentation rate, and serum C-reactive protein (CRP). Although serum CRP levels are usually normal, they may be slightly elevated up to 1.1–1.5 mg/dL in some patients (normal: <0.5 mg/dL). Serum prolactin and autoantibody (ANA and RF) assay should also be requested. The autoimmunity hypothesis warrants further assessment by immunological and serological tests to exclude an underlying autoimmune disorder (5, 48). In some cases, systemic lupus

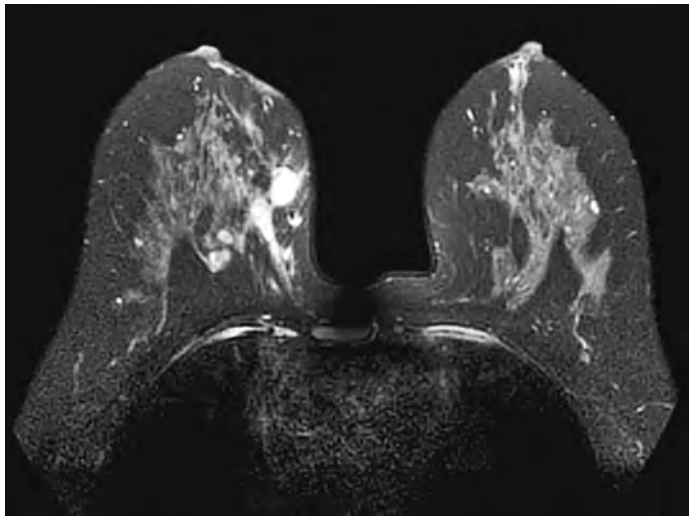

Figure 2. In breast MRI, on axial fat-suppressed T2W images, an oval-shaped, well-circumscribed cystic lesion in the middle of the right breast can be observed

erythematosus has been diagnosed in the presence of antineutrophil cytoplasmic (ANCA) and anti-dsDNA antibodies (5). A purified protein derivative test should also be performed, and in patients with suspected tuberculosis, tissue samples should be tested for mycobacterium tuberculosis, ideally by PCR (1, 3, 5, 10). Other investigations such as carcinoembryonic antigen and cancer antigen levels are expected to be within normal limits (5, 37).

A recent study on novel noninvasive biomarkers for GLM suggests that measuring circulating miR-155, let-7c, miR-21, and PTEN levels could be useful for distinguishing the condition from breast cancer (48). Researchers noted that miR-21 expression and PTEN levels were significantly elevated in BC compared to GLM. The authors reported that it would be useful to determine serum miR-21 and PTEN levels, which is a noninvasive method, in addition to traditional radiological methods, in differentiating IGM from BC (21, 48). This suggestion has yet to achieve international recognition and is not practical.

Imaging

There is a significant overlap between the imaging findings of GLM and malignant lesions of the breast. Many clinicians agree that ultrasound, elastography, Doppler ultrasonography, mammography, and magnetic resonance imaging (MRI) findings are not specific to GLM. Conversely, in practice, ultrasound (US) is accepted as the first-choice method in patients with suspected GLM. The presence of an irregular hypoechoic mass with an ill-defined margin, along with tubular extensions and tunneling, could be suggestive of GLM, and this could be complemented by compressive sonoelastography, where the lesion would show soft properties with low elasticity scores and strain ratios (49). Mammographic findings include focal asymmetry or an obscured mass (50). In clinical practice, MRI (Fig. 2) is one of the most preferred radiological methods in the effort to distinguish GLM from BC, and it is thought to have important contributions to showing active lesions and determining the extent of lesions. It may also help in evaluating possible residual disease after treatment and in monitoring the disease in patients receiving conservative treatment (50, 51).

Management

Watchful Waiting Strategy

Sometimes the cost of inaction, both therapeutically and financially, may outweigh the potential harms of the intervention. GLM can be self-limiting, and in many patients, spontaneous resolution has been reported without treatment. In a recent study, 50% of patients with GLM achieved complete remission at 2–24 months after disease onset, and the remaining 50% had no disease progression during the follow-up period (1). Similarly, complete remission was observed in 112 (93.33%) out of 120 patients with GLM surveyed between 2006 and 2019, with remission occurring within an average of 5 months (0–20 months) (52). Therefore, a "watchful waiting" strategy using clinical and imaging surveillance may be adopted in patients with a small breast mass as the only symptom. In the absence of other systemic symptoms, patients can be closely monitored for potential disease progression (1, 5, 6, 10).

Medical Treatment

Several approaches have been proposed for the medical management of GLM whether as primary treatment or as secondary treatment pre-and postsurgery.

Antibiotics

One of the most controversial issues in treatment is the routine use of antibiotics. Unfortunately, in daily practice, many surgeons may choose to prescribe antibiotics as first-line treatment. Antibiotics should not be routinely prescribed for GLM, and the decision should depend on the results of bacterial testing and drug susceptibility tests. Clindamycin, levofloxacin, and azithromycin may be prescribed empirically if there is a high level of suspicion, pending the results of antibiotic susceptibility testing (1, 53, 54).

Corticosteroids

Corticosteroids are like double-edged swords. It should be used at the right time and in the right dose. However, there are no standard dose and timing approach in this regard in the literature yet. GLM patients in the progressive stage with hyperemia and swelling may be treated with oral, intralesional (injection), and/or topical corticosteroids (1, 6, 10), the choice of which may depend on several factors such as the size of the lesion. Administration of corticosteroids before surgery may produce more favorable cosmetic outcomes for larger lesions. Conversely, GLM patients with predominately skin changes who develop adverse effects from oral corticosteroids may benefit from intralesional corticosteroid injection or topical steroids as viable alternatives (1, 55, 56). It should also be considered that topical use of steroids or superficial injections close to the skin may cause complications such as thinning of the skin. The duration of treatment with steroids needs to be adjusted according to the disease progression. Patients should be informed regarding the problems that may arise from the long-term use of steroids or the sudden termination of their use.

Noncorticosteroid Immunosuppressive Agents

A significant number of clinicians experience serious hesitation in using noncorticosteroid immunosuppressive agents. This is usually due to the lack of sufficient clinical observation and experience regarding the use of the aforementioned agents. Unfortunately, there is no consensus among clinicians regarding the timing and dosage of these agents. Each clinic acts according to its own experience.

Noncorticosteroid immunosuppressive agents, such as methotrexate (MTX) and azidothymidine (AZT), are considered second-line treatment options for GLM in patients who are resistant to or who require long-term use of corticosteroids. MTX is usually recommended at a dose of 5–15 mg/week for 6–24 months, and patients are advised to take two doses of folic acid per week before MTX use (57, 58). MTX should be avoided in women of childbearing age, and if used, contraception should be strongly advised. The main side effects of MTX treatment are liver and kidney impairment, and patients should be closely monitored for other adverse effects such as bone marrow suppression, folic acid deficiency, interstitial pneumonia, and gastrointestinal reactions (1, 57, 58). In a select group of patients, azidothymidine (AZT) may be an alternative option (1, 21, 59). The use of all of these agents requires extensive experience and knowledge regarding their side and unexpected effects.

Prolactin Inhibitors

The use of prolactin inhibitors, such as bromocriptine, may be recommended in GLM patients with confirmed elevated serum prolactin levels. If hyperprolactinemia develops as a result of an antipsychotic drug such as risperidone, an alternative should be considered in collaboration with a psychiatrist (1, 6, 18, 21, 23).

Surgical Treatment

Although it is thought that the origin of the disease is autoimmunity, trying to treat it with surgical methods leaves a question mark in the minds of researchers. The surgical treatment options should be discussed in detail with the patients. Patients should not consider surgical treatment as a miracle cure. Surgical resection is usually reserved for GLM patients with a prolonged course of the disease with systemic manifestations such as EN and polyarthritis or those who have recurrence after prior medical treatment. Reported recurrence rates of GLM are between 15.4% and 24.8% (1, 3, 5, 6, 8, 10). Recurrence should be confirmed by a Tru-cut biopsy and should be considered in patients with clinical or radiological evidence of an inflammatory mass (1, 3, 5, 21). Other indications include extensive distribution in three quadrants of the breast or the presence of acute or chronic complications such as complex abscesses, sinus and fistula formation, or chronic wound infection. Patients who do not respond to or are unable to tolerate medical treatment may also be candidates for surgery (1, 6, 10).

Wide local excision is generally accepted as the most effective option for lesions with small focus and very limited sinus or fistula tract and no abscess formation. Other alternative approaches depending on the extent of involvement include abscess excision and drainage, segmental resection, enlarged resection, and mastectomy (1, 5, 6, 43). Surgical treatment has been proven to have an acceptable cure rate and a relatively low recurrence rate with or without corticosteroids. A head-to-head comparison showed a cure rate of 90.6% with oral corticosteroids compared to 94.5% after surgery, with recurrence rates of 6.8% and 4.0%, respectively (60).

Although there are no specific absolute contraindications to surgery for GLM, it should be reconsidered in pregnant women, patients with complex extensive lesions involving more than two-thirds of the breast, wide area of skin lesions, and difficulties expected with postsurgical satisfactory recovery after surgery (3, 60). Similarly, surgery is generally avoided in GLM patients with signs of acute infection or those who are in a very advanced stage of the disease.

CONCLUSION

GLM is an infrequent, benign, inflammatory disease of the breast that mostly affects young women of reproductive age. Although a specific etiology of GLM has not been identified, hormonal disorders, autoimmunity, microbiological agents, genetic factors, smoking, and alpha-1 antitrypsin deficiency may have a role in the pathogenesis of the disease. A diagnosis of GLM requires the exclusion of other conditions such as breast cancer; tuberculosis; sarcoidosis; autoimmune conditions like Behçet's disease, Crohn's disease, Sjögren's syndrome, and systemic lupus erythematosus with granulomatosis and polyangiitis; diabetic mastopathy; and mammary duct ectasia. The management of GLM may be medical or surgical. Surgical resection is usually reserved for GLM patients with a prolonged course of the disease and systemic manifestations such as EN and polyarthritis or those who have recurrence after prior medical treatment. Other indications for surgery are extensive distribution in three quadrants of the breast; the presence of acute or chronic complications such as complex abscesses, sinus, and fistula formation; chronic wound infection; and intolerance to medical treatment. The symptoms and signs of GLM are not specific, and the rarity of the condition means that clinical experience is limited. Conversely, clinicians should be aware of GLM and its diagnosis and treatment.

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