Benign Breast Disease

Periareolar Mastitis, Granulomatous Lobular Mastitis, and Lymphocytic or Diabetic Mastopathy

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KEYWORDS

• Periareolar mastitis • Granulomatous lobular mastitis • Diabetic mastopathy

KEY POINTS

- The operative management of periareolar mastitis consists of central duct excision, excision of the site of the abscess at the periareolar margin, and reconstruction of the subareolar complex.
- The authors' current treatment strategy for granulomatous lobular mastitis avoids surgical procedures in favor of aspiration of abscesses, management with short courses of antibiotics, and even observation for the treatment of milder cases of granulomatous mastitis.
- Diabetic mastopathy occurs in patients with long-standing insulin-dependent diabetes, especially those with microvascular complications such as retinopathy, nephropathy, or neuropathy. If the diagnosis can be confirmed by core needle biopsy, surgical excision can generally be avoided.

INTRODUCTION

Although the surgical treatment of *malignant* diseases of the breast is an important component of patient outcome, there are times when the technical elements of procedures for *benign* inflammatory breast conditions are underappreciated, clinically vexing, and can lead to significant morbidity when underperformed; this is certainly true for periareolar mastitis, granulomatous lobular mastitis, and lymphocytic or diabetic mastopathy, where understanding the pathophysiology is a key to success in the surgical management of these conditions.

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PERIAREOLAR MASTITIS

Periareolar mastitis is also known by its synonyms periductal, subareolar, and plasma cell mastitis. It is an uncommon benign inflammatory condition of the breast that causes frustration for many patients, and its pathophysiology is misunderstood by many surgeons. Seminal clinical observations regarding diagnosis and surgical management have been provided by some of the leaders of breast surgery from previous generations, including Urban,[1] Scanlon,[2] and more recently Lannin.[3]

Clinical Presentation and Initial Treatment

Periareolar mastitis frequently presents as a recurrent abscess or sinus at the areolar margin in women in their 20s and 30s (**Fig. 1**). Although the disease process can occur in men, it is exceedingly uncommon in our experience. It is not unusual to see patients who have had either a previous incision and drainage of abscess without accompanying definitive surgical treatment or a prior breast biopsy revealing duct ectasia. Duct ectasia is a manifestation of chronic duct obstruction and is a nonspecific finding that may be associated with multiple etiologies.

The pathognomonic findings on clinical examination are erythema and edema involving the periareolar margin and a transverse cleft in the nipple itself. At times, there is enough edema in the areolar skin that the transverse cleft is not identifiable at the time of presentation, only being appreciated when the edema and erythema have somewhat resolved after initial treatment with antibiotics or drainage of an

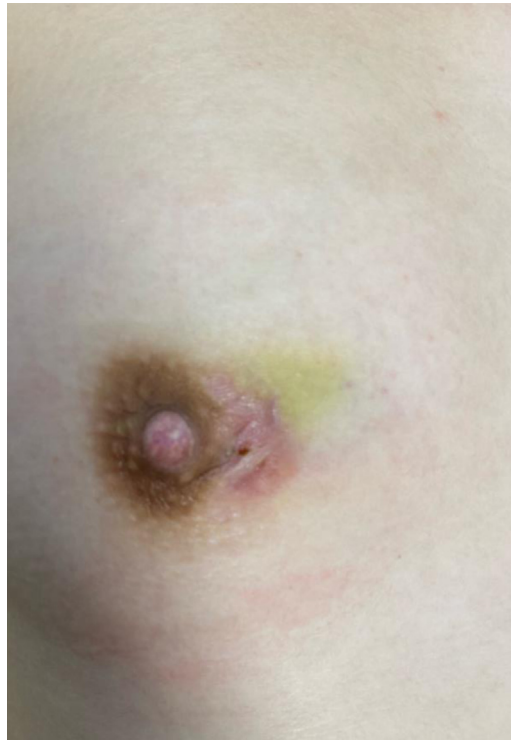

Fig. 1. Periareolar mastitis. Patient presented with 2-year history of exacerbations and remissions of inflammation at the periareolar margin, now with a chronic lactiferous sinus.

abscess. Imaging with ultrasound is preferred and demonstrates a mass within the central duct with postobstructive duct ectasia in the subareolar duct system.

Initial treatment usually consists of a short course of antibiotics and aspiration of abscess to reduce the inflammation enough so that a definitive surgical procedure can be done. Persistent or recurrent abscess may occasionally require incision and drainage, which, if necessary, should be done using only a periareolar incision to facilitate the reconstruction of the subsequent surgical defect incurred during the definitive surgical excision.

Pathophysiology and Surgical Management

The hallmark pathologic finding is squamous metaplasia of the epithelial lining of the central duct within the nipple causing major duct obstruction and subareolar duct ectasia.[4] An association between cigarette smoking and the development of squamous metaplasia has previously been described.[5] The mechanical obstruction of the central duct causes dilatation of the subareolar ducts and sets up a vicious cycle of periductal inflammatory response, infection, and further duct obstruction. However, it is not known what percentage of women with a transverse cleft in the nipple never develop a clinical infection. Antibiotics, aspiration, and incision and drainage of abscess do not address the cause of the central duct obstruction, so it is not surprising that these therapeutic maneuvers in the absence of central duct excision are associated with a disease process characterized by exacerbations and recurrence of abscess. If the condition becomes chronic, there is occasionally a periductal infiltration of plasma cells, leading to the so-called plasma cell mastitis. It is also appreciated that not all patients who have initial treatment with antibiotics and aspiration of abscess develop a recurrence of periareolar mastitis requiring central duct excision. Indeed, Lannin reported that only about one-half of patients developed a recurrent abscess after management of the first episode with antibiotics and aspiration of abscess.[3]

Indications for surgical management include persistent lactiferous duct fistula, recurrent subareolar abscess, or a residual mass remaining after needle aspiration and antibiotics. The operative management consists of central duct excision, excision of the site of the abscess at the periareolar margin, and reconstruction of the subareolar complex. Urban[1] described a radial incision, and Lannin[3] favored removing an ellipse of skin in a radial fashion. Scanlon[6] popularized the concept of "diamond biopsy," in which the central major duct, a portion of the skin of the areola and breast including the site of the abscess, and subareolar complex are excised (**Fig. 2**). The reconstructed nipple-areolar complex retains a reasonably natural appearance (Edward F. Scanlon, MD, 1977–1982, Evanston Hospital, Evanston, ILL, personal communications) (**Fig. 3**). We continue to use the "diamond biopsy" in current-day practice.

Recurrence of periareolar mastitis after definitive duct excision is highly unusual. Interesting enough, in our experience and confirmed by Lannin,[3] the development of periareolar mastitis in the contralateral breast is also uncommon.

GRANULOMATOUS LOBULAR MASTITIS

Granulomatous lobular mastitis (GLM) is an uncommon but challenging group of benign inflammatory diseases of the breast, requiring careful management of provider and patient expectations.

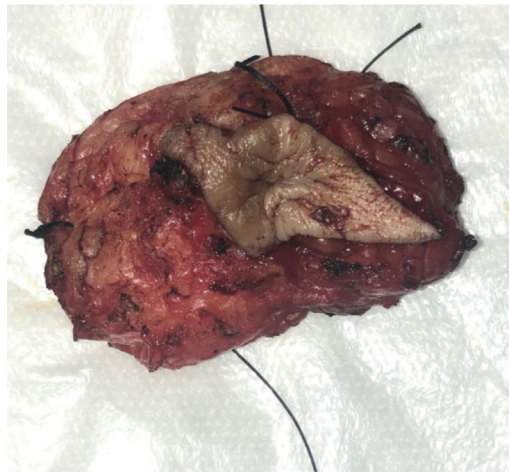

Fig. 2. "Diamond biopsy" includes excision of the central duct, the site of the abscess at the periareolar margin, and subareolar complex.

Clinical Presentation and Initial Evaluation

There have been many publications on GLM from Turkey, and in the United States greater than 90% of patients identify ethnically as Hispanic, leading some investigators to suggest that GLM has a Mediterranean origin. Patients most commonly present with a palpable breast mass at a median age of 35 years and with a recent history of pregnancy.[6] As GLM becomes a chronic condition, there is a characteristic discoloration of the skin overlying the breast mass.

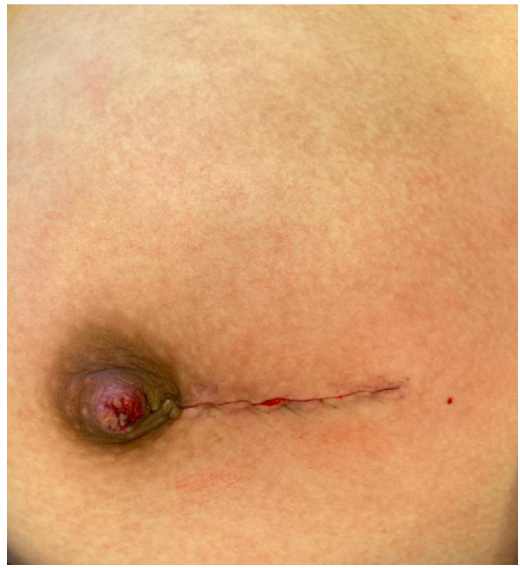

Fig. 3. Reconstructed nipple-areolar complex after excision of the central duct, skin with periareolar abscess, and subareolar complex.

Imaging should include breast ultrasound, which typically demonstrates a hypoechoic mass with features similar to those seen in carcinoma of the breast, so core needle biopsy is essential to distinguish the difference between GLM and cancer. The hallmark pathologic finding of GLM is the presence of noncaseating granulomas centered around breast lobules. Acid-fast bacillus and Grocott methenamine silver stains exclude tuberculosis and fungi as causes of GLM. A thorough review of the patient's history and physical examination should be done to exclude other diseases associated with breast granulomas, such as histoplasmosis, sarcoidosis, foreign body reaction, and collagen vascular diseases (Sjogren syndrome and erythema nodosum).

Treatment of Granulomatous Lobular Mastitis and Idiopathic Granulomatous Mastitis

Cases of GLM with identifiable causes have defined treatment criteria, but those without identifiable causes are generally referred to as idiopathic granulomatous mastitis (IGM). Most patients presenting with GLM will be designated as having IGM, as demonstrated in a recent report of GLM in which only 4% of patients had co-existing autoimmune diseases.[6] Despite having been first described by Kessler and Wolloch[7] in 1972, the lack of consensus on the cause of IGM has led to multiple treatment options, ranging from observation to medical treatment with steroids, bromocriptine, methotrexate, and antibiotics to aspiration of fluid collections to surgical interventions, such as incision and drainage, excision, and even mastectomy.[8–15]

In our experience treating 285 patients with GLM from 2008 to 2018 at a large urban safety-net medical center, the treatment algorithm evolved over the 10-year period.[6] Because of unfavorable cosmetic outcomes with surgical management in our early experience, the preferred treatment of fluid collections and abscesses became aspiration instead of incision and drainage. Fine-needle aspiration can be performed by the surgeon at the bedside with or without ultrasound guidance. Also, the use of steroids became reserved for patients with diseases for which steroids were the appropriate initial management instead of being used more liberally for patients with large areas of breast involved with IGM, refractory to 4 to 6 weeks of antibiotic therapy.

For the patients in this series, once the diagnosis of IGM was confirmed by core needle biopsy, 17% of patients had no treatment, 22% had aspiration (± medical treatment, defined as a short course of antibiotics consisting of oral trimethoprim/sulfamethoxazole and metronidazole, and nasal mupirocin), 35% had medical treatment alone, and 27% had surgical intervention (± medical treatment). The overall median duration of disease was 16 weeks, and for patients treated by aspiration (± medical treatment) or medical treatment alone it was not significantly different than for those who were observed without treatment. However, disease duration was significantly longer for patients who had surgical intervention (± medical treatment) than for those who were observed. Patients requiring surgical intervention probably had more severe cases of IGM than those in the other treatment groups, resulting in more protracted courses of disease. The overall recurrence rate was 22%. Compared with patients who were observed, the recurrence rate was not significantly higher for patients who had aspiration (± medical treatment) or for those who received medical treatment alone, but it was significantly higher for patients who had surgical intervention (± medical treatment). The findings of this study appeared to justify our current treatment strategy of avoiding surgical procedures in favor of aspiration of abscesses, management with short courses of antibiotics, and even observation for the treatment of milder cases of IGM. However, one of the more difficult problems associated with this treatment algorithm was managing the understandable frustration of patients and

providers during multiple recurrences of erythema and abscess, while resisting the temptation to use incision and drainage procedures.

Identifying the cause of IGM has remained elusive. It has been appreciated more recently that the microbiome can make significant contributions to granulomas. Next-generation sequencing and polymerase chain technologies have allowed the identification of multiple species-specific bacterial and fungal signatures within granulomas.[16–18] However, the significance of identifying these organisms within granulomas remains to be clarified.

LYMPHOCYTIC OR DIABETIC MASTOPATHY

Lymphocytic mastopathy is an uncommon breast condition that presents with single or multiple clinical masses or mammographic densities. It is thought that the process is probably immune-mediated, as the masses are microscopically associated with dense perilobular and perivascular lymphocytic (mainly B-cell) infiltrates, lobular atrophy, and dense stromal fibrosis.[19] The lymphocytic infiltrate is often accompanied by stromal epithelial myofibroblasts, which can lead to a mistaken diagnosis of invasive carcinoma, granular cell tumor, or Rosai-Dorfman disease. This condition is most common in women with insulin-dependent (type 1) diabetes.[20] However, cases with similar pathologic features may occur in the absence of diabetes mellitus, such as in women with autoimmune thyroid disorders. Thus, a general pathologic term, "sclerosing lymphocytic lobulitis" or "lymphocytic mastopathy," may be preferable to "diabetic mastopathy."[21]

Historical Background for Diabetic Mastopathy

Diabetic mastopathy is an uncommon disease process seen in premenopausal women with long-standing type I diabetes mellitus. The condition was first described by Soler and Khardori in 1984, who studied 12 female patients with insulin-dependent diabetes, limited joint mobility (cheiroarthropathy), thyroiditis, and painless fibrous breast masses.[22] The investigators suggested that because of a relationship between cheiroarthropathy and the effect of hyperglycemia on connective tissue, fibrous breast masses may represent another manifestation of connective tissue disease. They also noted similar appearances between the lymphocytic infiltrates in the fibrous breast masses and those seen in the patients with Hashimoto thyroiditis. In this study, there was no relationship between any human leukocyte antigen histocompatibility subtype and cheiroarthropathy.

In 1987, Byrd and colleagues[23] described the distinct pathologic features of biopsies done for "mastopathy in insulin-dependent diabetics" as dense fibrosis with increased fibroblasts and perivascular lymphocytic infiltrates. Notably, no patients had duct hyperplasia, changes in their epithelial cells, or findings that suggest malignancy. In 1992, Tomaszewski and colleagues[24] coined the term "diabetic mastopathy" and further characterized the pathologic findings of breast masses in patients with long-standing diabetes. They demonstrated that the lymphocytic perivascular infiltrates were composed primarily of B cells and that there was a dense keloid-like fibrosis containing "epithelioid fibroblasts," which appeared to be unique to patients with diabetes. The epithelioid fibroblasts were thought to be an unusual form of myofibroblast known to contain muscle-specific actin and to stain positive for a pan B-cell marker (MB2) on immunostaining studies.

In 2000, Camuto and colleagues[25] proposed 4 diagnostic criteria for diabetic mastopathy: (1) premenopausal woman with long-standing type I diabetes mellitus with associated microvascular complications, such as diabetic retinopathy, neuropathy,

or nephropathy; (2) a firm, nontender breast mass identified on clinical breast examination, clinically suspicious for carcinoma; (3) mammographic and ultrasonographic findings of increased density, but without a discrete mass; and (4) excisional or core needle biopsy showing dense keloidal fibrosis associated with periductal or perilobular lymphocytic infiltrate, with or without epithelioid fibroblasts.

Clinical Presentation

Patients with diabetic mastopathy are premenopausal women in their 30s to 40s with insulin-dependent diabetes, who present with one or more painless, well-defined breast masses, although there can be variable examination findings.[25] Although most patients have type I diabetes, there have also been cases reported in patients with type II diabetes. Patients commonly have another complication of long-standing disease, such as nephropathy, neuropathy, or retinopathy. Patients can present with unilateral or bilateral masses and typically do not have lymphadenopathy. Although the masses are benign, they are often clinically indistinguishable from breast cancer on examination or imaging, which leads to core needle or excisional breast biopsies to make a tissue diagnosis. Following initial evaluation, patients can develop recurrences that may be larger in size. In one patient case series, 3 of the 5 patients developed a recurrence, commonly within 1 year of diagnosis.[24]

Several studies have proposed diagnostic criteria for diabetic mastopathy.[24–26] Most of these criteria include a history of long-standing insulin-dependent diabetes mellitus, at least one firm breast mass, imaging showing at least one area of increased density, and a biopsy demonstrating keloidal fibrosis.

Pathophysiology

The pathophysiology of diabetic mastopathy remains incompletely understood and is likely multifactorial. It has been proposed that exogenous insulin use may contribute to the formation of the breast masses, as the affected population is almost universally insulin dependent. Others have proposed that hyperglycemia leads to the production of nonenzymatically glycosylated proteins that resist degradation and accumulate in breast tissues.[25,27,28] These proteins may function as neoantigens, which leads to an autoimmune response, B-cell proliferation similar to that seen in other autoimmune conditions, and eventual cytokine release by macrophages.[24]

Imaging

Because of clinical suspicion for underlying malignancy, patients with diabetic mastopathy frequently require imaging to further elucidate the diagnosis. Mammography and ultrasound are the preferred imaging modalities for excluding malignancy.[29] Mammography demonstrates dense parenchyma without a discrete mass, architectural distortion, or calcifications. Ultrasound reveals ill-defined hypoechoic areas with characteristic acoustic shadowing that is more pronounced than that seen with malignancy, likely secondary to fibrosis.[26] Ultrasound can also be useful for image-guided biopsies and monitoring. Computerized tomography (CT) or MRI are unlikely to add valuable information or change management.[27] Imaging findings are not specific enough to yield a diagnosis; therefore, most patients subsequently undergo biopsy.

Pathologic Features

Because of the fibrotic nature of the masses, fine-needle aspiration often does not provide sufficient tissue for diagnosis.[23,26] Therefore, patients should undergo core needle biopsy and if necessary, subsequent excisional biopsy to make a definitive diagnosis.

Grossly, masses associated with diabetic mastopathy are distinct from the surrounding breast tissue, homogeneous, and firm with a tan-white hue. Microscopic examination reveals dense fibrosis with associated perivascular, periductal, and perilobular lymphocytic infiltrates. Importantly, there is no evidence of hyperplasia or malignancy. As mentioned earlier, Tomaszewski and colleagues[24] described the pathologic findings characteristic of diabetic mastopathy: (1) lymphocytic lobulitis and ductitis with glandular atrophy; (2) lymphocytic/mononuclear perivascular inflammation, predominantly B cell; (3) dense, keloid-like fibrosis; and (4) epithelioid-like fibroblasts. This study was the first to describe epithelioid fibroblasts as rounded epithelioid cells with abundant cytoplasm and oval vesicular nuclei, and the investigators proposed that their presence was pathognomonic of diabetic mastopathy. However, Seidman and colleagues[28] later demonstrated that epithelioid fibroblasts were not essential for the diagnosis of diabetic mastopathy.

Management

Because diabetic mastopathy is a benign condition, not associated with increased risk of subsequent breast cancer, there are no specific interventions recommended after the diagnosis has been confirmed. In most cases, the diagnosis can be made by coupling a high index of suspicion with core needle biopsy, thereby avoiding the need for excisional biopsy. However, the dense fibrosis can make it difficult to obtain enough tissue for accurate diagnosis by core needle biopsy.

At this time, there are no differences in breast cancer screening guidelines for those with diabetic mastopathy compared with women at average risk of developing breast cancer. Patients should be advised that they may develop subsequent breast masses in either breast, even after surgical excision. Because new breast masses could represent breast malignancy, they should not be presumed to be diabetic mastopathy but should undergo standard evaluation with mammogram, ultrasound, and core biopsy, if necessary.

SUMMARY

The operative management of periareolar mastitis consists of central duct excision, excision of the site of the abscess at the periareolar margin, and reconstruction of the subareolar complex.

The investigators' current treatment strategy for granulomatous lobular mastitis avoids surgical procedures in favor of aspiration of abscesses, management with short courses of antibiotics, and even observation for the treatment of milder cases of granulomatous mastitis.

Lymphocytic or diabetic mastopathy occurs in patients with long-standing insulin-dependent diabetes, especially those with microvascular complications such as retinopathy, nephropathy, or neuropathy. Once the diagnosis has been confirmed by core needle biopsy, surgical excision can generally be avoided.

CLINICS CARE POINTS

- When being consulted to manage an erythematous breast, the first consideration is to distinguish routine breast abscess from inflammatory breast cancer, periareolar mastitis, or granulomatous mastitis.
- The pathognomonic findings of periareolar mastitis on clinical examination are the presence of the abscess at the areolar margin and a transverse cleft in the nipple.

- After initial management of periareolar mastitis with fine-needle aspiration and oral antibiotics, a decision must be made on whether central duct excision is necessary.
- Because granulomatous lobular mastitis and diabetic mastopathy have clinical and radiographic features similar to carcinoma of the breast, ultrasound-guided core needle biopsy is essential to establish an accurate diagnosis.

DISCLOSURE

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