Diabetic Mastopathy

A Clinicopathologic Review

Kim A. Ely, MD,[1] Gary Tse, MB BS,[2] Jean F. Simpson, MD,[1] Rick Clarfeld, MD,[3] and David L. Page, MD[1]

Key Words: Diabetic mastopathy; Diabetes; Ductitis; Lobulitis; Vasculitis

Abstract

Diabetic mastopathy, an uncommon form of lymphocytic mastitis and stromal fibrosis, typically occurs in longstanding type 1 diabetes. Nineteen cases meeting predetermined histopathologic criteria for diabetic mastopathy were correlated as to clinical history and disease recurrence. Physical examination revealed palpable discrete masses or diffuse nodularity, both predominantly in the subareolar region. One nonpalpable lesion was detected incidentally during reduction mammoplasty. All cases contained lymphocytic ductitis and lobulitis with varying degrees of keloidal fibrosis, vasculitis, epithelioid fibroblasts, and lymphoid nodule formation. Single mammary lesions were found in 11 patients with type 1 diabetes, 1 with type 2 diabetes, and 3 without diabetes. Four cases were bilateral (3 patients with type 1 and 1 patient with type 2 diabetes). Six of 19 cases recurred (3 ipsilateral, 2 contralateral, and 1 bilateral). We confirm the histopathologic constellation for diabetic mastopathy. However, we question the specificity of these features because of identical findings in patients with type 2 diabetes and nondiabetic patients. We found diabetic mastopathy in men and women, as a solitary mass or bilateral disease, and recurrence in either breast, sometimes multiple. Recognition of potential recurrence is important because it might spare patients with documented diabetic mastopathy from repeated breast biopsies.

An association between diabetes mellitus and fibrous breast disease was reported initially in 1984 by Soler and Khardori,[1] who described 12 patients with longstanding type 1 diabetes mellitus, multiple diabetic complications, and palpable breast masses. Three years later, the term *diabetic mastopathy*[2] was coined for the combination of connective tissue overgrowth with perivascular lymphocytic infiltrate characteristic of this lesion. As similar histopathologic features may be seen in patients with autoimmune disease,[3-5] Tomaszewski et al[6] proposed defining microscopic and clinical criteria that uniquely describe diabetic mastopathy. According to their report, although lymphocytic lobulitis, ductitis, and vasculitis occasionally may be encountered in nondiabetic breast biopsy specimens, distinctive epithelioid cells (epithelioid fibroblasts) set within a densely fibrous stroma seem unique to the diabetic condition.

While the microscopic features of diabetic mastopathy have been well documented,[6,7] few reports have addressed the natural history of this lesion with regard to recurrence after biopsy.[6,8-10] We followed up 19 cases (representing type 1 diabetes, type 2 diabetes, and no diabetes) that met the currently accepted criteria for diabetic mastopathy for up to 14 years. The incidence of recurrence in either breast is described, as is the relationship between diabetic mastopathy and its clinical associations.

Materials and Methods

The breast consultation archives of Vanderbilt University Medical Center, Nashville, TN, were searched for the pathologic diagnosis of diabetic mastopathy given between January 1984 and July 1998. Eighteen cases with the

accompanying clinical history and follow-up were identified. The computerized files from the surgical pathology department of Vanderbilt University Medical Center were searched by the key words *diabetic mastopathy, fibrous mastopathy,* and *chronic mastitis* during a similar interval. Four additional cases with corresponding demographic data were retrieved. All of the available H&E-stained slides were reviewed in a blinded fashion by 3 authors (K.A.E., G.T., and D.L.P.). The slides were evaluated for the presence of lymphocytic ductitis, lymphocytic lobulitis, lymphoid nodule formation with or without germinal center formation, mononuclear vasculitis, epithelioid fibroblasts, and keloidal fibrosis. As defined by Seidman et al,[7] the latter required involvement of at least a 5-mm area by thick alternating bands of collagen.

Patient clinical information was obtained through 2 modes. Consultation data were collected via submission of a detailed questionnaire to the referring pathologist and, when necessary, through telephone contact with the respective surgeons and primary care physicians. Demographic data from the cases processed through the surgical pathology department at Vanderbilt University Medical Center were obtained by medical chart review. Information was gathered on patient age and sex, diabetic history with regard to type (type 1or 2), duration of illness, therapy, and complications of diabetes. In addition, information on previous breast lesions or subsequent development of masses was sought.

Results

A total of 22 cases with diagnoses of diabetic mastopathy, fibrous mastopathy, and chronic mastitis were retrieved. H&E-stained slides were available for review for 20 cases; the number of glass slides ranged from 1 to 15 per case (mean, 3.5 slides). Nineteen of 20 cases demonstrated histologic evidence of lymphocytic ductitis or lobulitis **Image 1** and **Image 2**, keloidal fibrosis, and perivasculitis (diabetic mastopathy). While ductitis was present universally, lobulitis was present only in the female breast. This is an expected finding as the male breast lacks lobules. In many cases (13 [68%]), dense collections of lymphocytes in close association with vessels, atrophic ducts, or both, and lacking germinal centers **Image 3** were observed. Epithelioid fibroblasts **Image 4**, first described by Tomaszewski et al[6] as large plump fibroblasts that show a mild degree of pleomorphism, also were a frequent feature (14 [74%]). In some cases, they were arranged in a whorled, vaguely nodular pattern.

The 19 cases represented 15 from the consultation service and 4 from the Vanderbilt University Medical Center surgical pathology files. The study group **Table 1** included 17 women and 2 men with ages ranging from 27 to 75 years (mean ± SD, 39 ± 12). Fifteen patients had a single mammary lesion when first examined, and 4 had bilateral disease. The breast lesions were characterized on physical examination as palpable discrete masses (n = 17) or as diffuse nodularity (n = 1). An additional case was discovered during bilateral reduction mammoplasty. In 7 (37%) of 19 cases, localization of the lesion to the subareolar region was reported.

A history of diabetes was elicited in 16 cases (type 1, 14 cases; type 2 insulin-requiring, 1 case; and type 2 non–insulin dependent, 1 case). Three patients had no diabetic history. Of the cases of type 1 diabetes, the exact duration was known in 12 and ranged from at least 15 to 36 years. Secondary complications were determined in 11 of 14 cases of type 1 diabetes, including retinopathy, 8 cases; nephropathy, 6 cases; and neuropathy, 3 cases. Seven patients were hypertensive, and 2 of these patients had undergone kidney transplantation. One patient with type 1 diabetes had hypothyroidism; however, no other patients had clinical evidence of possible autoimmune disease. Epithelioid fibroblasts were observed in 14 cases (11 with type 1 diabetes and 3 without diabetes). They were absent in both men.

Six women (5 with type 1 and 1 without diabetes) had biopsy-proven recurrence. This represented 1 bilateral recurrence, 1 ipsilateral recurrence, 1 ipsilateral recurrence that recurred twice, 1 ipsilateral occurrence that recurred thrice, 1 contralateral recurrence, and 1 contralateral recurrence that recurred twice. Physical examination revealed 2 additional patients recurrences; however, subsequent biopsy was not performed to further characterize these changes.

Discussion

Since the first description of fibrous breast lesions in diabetic patients, known as diabetic mastopathy, in 1984,[1] several series[2,6,7] have attempted to define and confirm the histologic features that specifically identify diabetic mastopathy. In 1992, Tomaszewski et al[6] studied 8 patients with longstanding type 1 diabetes with breast masses and compared them with nondiabetic patients or patients with diabetes of short duration with fibrosis and chronic mastitis. The former cases contained lymphocytic lobulitis and ductitis, vasculitis, and dense keloidal fibrosis that in 6 cases demonstrated epithelioid fibroblasts. The control group did not have the complete constellation of changes. Seidman et al[7] subsequently tested the specificity of these findings in patients with diabetes and age-matched control subjects. They identified 5 insulin-requiring diabetics (type 1, 2 cases; type 2, 3 cases) with extensive keloidal fibrosis, mononuclear perivasculitis, and mononuclear ductitis, and/or lobulitis, whereas none of the cases with non–insulin-requiring type 2 diabetes or control

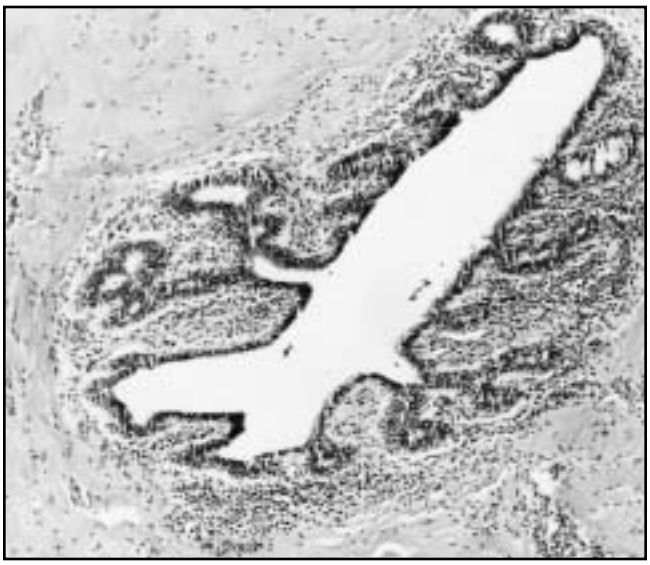

Image 1 Collections of lymphocytes surrounding a mammary duct (H&E, ·25).

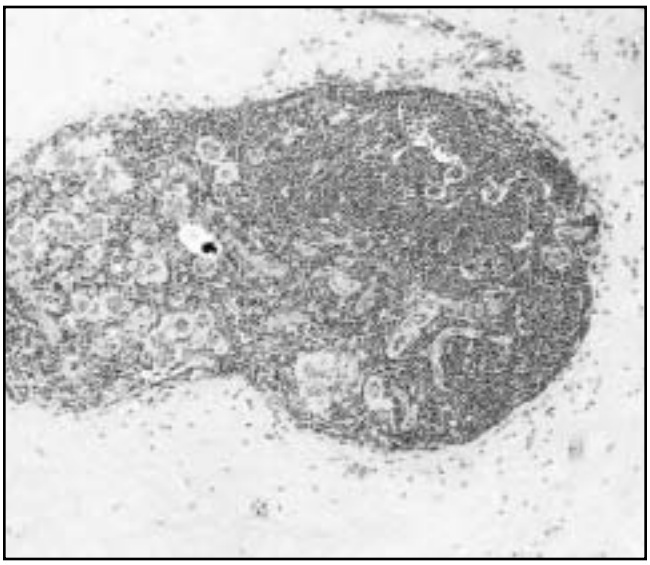

Image 2 Dense infiltrate of small, mature lymphocytes affecting a lobular unit (H&E, ·25).

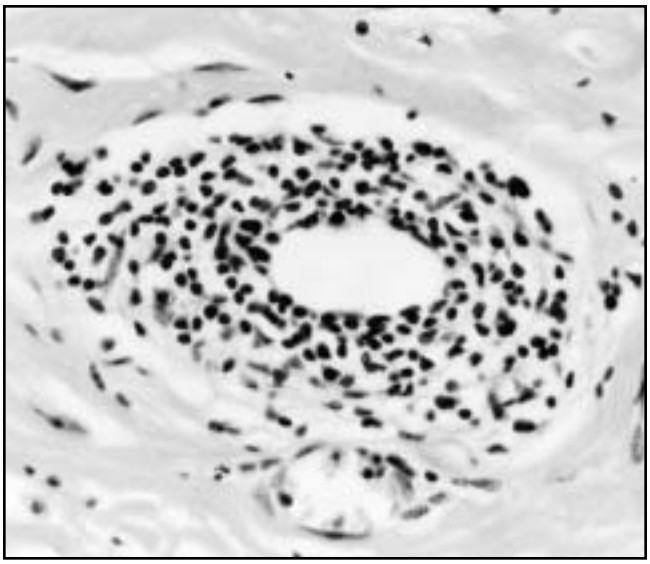

Image 3 An aggregate of lymphocytes in association with a blood vessel (H&E, ·40).

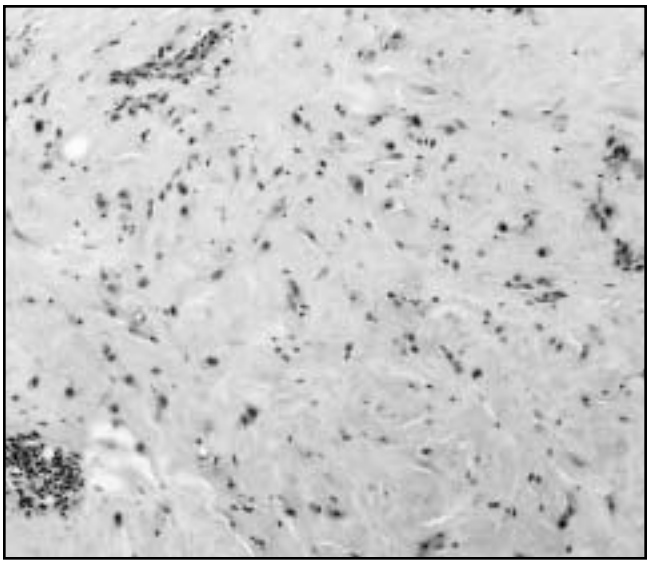

Image 4 Vaguely nodular arrangement of epithelioid fibroblasts set within a fibrous stroma (H&E, ·25).

subjects had all of these features.[7] Epithelioid fibroblasts were present in 3 of their 5 cases but did not seem essential for making the diagnosis. In the present study, which represents the largest series of patients, we found cases meeting the proposed histopathologic criteria for diabetic mastopathy[6] and correlated them with the underlying clinical condition and mode of presentation. The patients were followed up for up to 14 years after biopsy to study the natural history of the lesion with regard to recurrence.

All 19 of our cases displayed evidence of lymphocytic ductitis or lobulitis, keloidal fibrosis, and perivasculitis on breast biopsy. Similar to other reports,[5,6] diabetic mastopathy occurred in men and women, underscoring the need for awareness of this lesion in the male diabetic population. As noted, the insulin-requiring diabetics had disease of long duration (>15 years) and a high rate of secondary complications.

Unique to our study is the percentage of lesional recurrences and the number of patients with bilateral disease. Four cases (21%) manifested as synchronous bilateral breast masses. These demonstrated histologic features similar to and the same predilection for a subareolar location as those with unilateral disease. The recurrence rate in our series was 32%. Recurrences were ipsilateral, contralateral, or bilateral. In some instances, they were multiple,

Table 1
Clinical Data for Patients With Diabetic Mastopathy

Case No./Sex/ Age (y)	Diabetic History and Other Clinical Data	Secondary Complications	Epithelioid Fibroblasts	Recurrence
1/F/40	Type 1, 36 y; HTN	Retinopathy	Absent	None
2/F/34	Type 1, 17 y; HTN	Retinopathy, nephropathy	Present	None
3/F/46	Type 1, 17 y; HTN	Nephropathy	Present	None
4/F/36	Type 1, 15 y	Retinopathy	Absent	None
5/F/31	Type 1, 25 y; HTN, renal transplant	Nephropathy, neuropathy	Present	Ipsilateral, 2
6/F/30	Type 1, longstanding; HTN, hemodialysis	Retinopathy, nephropathy	Present	Ipsilateral, 1
7/F/36	Type 1, 20 y; HTN, renal and pancreatic transplants	Retinopathy, neuropathy	Present	None
8/F/47	Type 1, 31 y	Retinopathy	Present	Contralateral, 1
9/M/75	Type 2, insulin for 7 y; HTN	Nephropathy	Absent	None
10/M/38	Type 1, 34 y	Unknown	Absent	None
11/F/31	Type 1, 26 y	Unknown	Present	Ipsilateral, 3
12/F/59	Type 1, 30 y	Retinopathy	Present	None
13/F/29	Nondiabetic	None	Present	Contralateral, 2
14/F/32	Nondiabetic	None	Present	None
15/F/51	Nondiabetic	None	Present	None
16/F/30*	Type 1, longstanding; hypothyroidism	Unknown	Present	Bilateral, 1
17/F/27*	Type 1, 17 y; HTN, renal transplant	Retinopathy	Present	None
18/F/33*	Type 2, 2 y	None	Absent	None
19/F/36*	Type 1, 30 y	Neuropathy, nephropathy	Present	None

HTN, hypertension.
* Bilateral mammary disease at first examination.

occurring 2 and 3 additional times. Usually the recurrences developed within 5 years of the initial diagnosis; keloidal fibrosis dominated the microscopic picture. Recognition of this capacity for disease recurrence is important as it might help to avoid repeated breast biopsy. In fact, Rollins[11] recommends that in a patient with a prior diagnosis of diabetic mastopathy, the lesion be assessed by fine-needle aspiration. If the cytologic and clinical findings are consistent with diabetic mastopathy, conservative clinical management could be considered.

The inclusion of 3 nondiabetic cases and 1 non–insulin-dependent type 2 diabetic case with microscopic characteristics of diabetic mastopathy adds further to the interesting findings from our series. This constellation of features occurring outside the setting of insulin-requiring diabetes mellitus is in contradistinction to previous reports.[6,7] Although this set of histopathologic criteria can be observed in association with autoimmune disease in the absence of diabetes,[3,4] the non–insulin requiring type 2 diabetic case and the nondiabetic cases in our study had no clinical evidence of an autoimmune process. Surprisingly, epithelioid fibroblasts, believed to be specific for diabetic mastopathy,[6] also were seen in our patients without a diabetic history. Similarly, in their series of 14 biopsies, Ashton et al[5] found examples of epithelioid-type cells in nondiabetic patients with systemic lupus erythematosus and hypothyroidism. They concluded that epithelioid stromal cells are not unique to patients with insulin-dependent diabetes mellitus.[5] Thus, it seems that the proposed features are not as specific as previously maintained, or the appearance of diabetic mastopathy in the breast may precede the onset of clinical diabetes or another autoimmune processes. It may even be that some patients with this compilation of histopathologic findings will never develop diabetes or an autoimmune illness. The situation might be analogous to recent observations made by O'Toole et al[12] about the relationship between diabetes mellitus–glucose intolerance and necrobiosis lipoidica. They concluded that necrobiosis lipoidica can be associated with diabetes mellitus, but only a minority of patients develop the disease.[12]

Although the pathogenesis of diabetic mastopathy remains unknown, several mechanisms have been suggested. Seidman et al[7] proposed that exogenous insulin might lead to the development of diabetic mastopathy through an inflammatory or immunologic reaction to insulin, the vehicle, or a contaminant in the vehicle. The observations made in the present case series with bilateral presentations and multiple recurrences would indicate a systemic cause rather than a local event. It is known that

among the metabolic disturbances in diabetes, matrix expansion may occur.[13,14] Tomaszewski et al[6] hypothesized that these fibroinflammatory lesions were attributable to extracellular matrix expansion secondary to increased collagen production and decreased degradation, in part related to the hyperglycemic state. According to their model, advanced glycosylated end products are formed and act as neoantigen, triggering an autoimmune response with B-cell proliferation and autoantibody production. The resultant cytokine release would lead to matrix expansion.

The role of autoimmunity in the cause of diabetic mastopathy first was suggested by Soler and Khardori.[1] They observed a link between diabetes, thyroid disease, and connective tissue abnormalities. Interestingly, HLA-DR3, HLA-DR4, and HLA-DR5 were expressed in cases in their study. Such expression of these class II human leukocyte antigens has been associated with autoimmune disease.[15] Furthermore, while normal nonlactating breast epithelium lacks major histocompatibility complex class II products, they are seen in the epithelium of inflamed lobules.[3] These inflamed lobules also are very reminiscent of the lymphoepithelial lesions seen in other autoimmune diseases such as Hashimoto thyroiditis and Sjögren syndrome.[3,4]

Although many mechanisms have been offered about the cause of diabetic mastopathy, none has been proven. While some of the discussed theories may explain the findings in a setting of hyperglycemia and exogenous insulin use, an autoimmune basis would best address their presence outside this population. As mentioned, the set of histopathologic criteria used to define diabetic mastopathy may be seen in other autoimmune diseases. Lammie et al[3] reported stromal sclerosis and chronic perivasculitis and perilobulitis in a patient in whom Hashimoto thyroiditis subsequently developed. It may be that after continued clinical follow-up, our patients without a diabetic history eventually will manifest diabetes mellitus or another autoimmune condition.

While our study confirms the histopathologic features for diabetic mastopathy, we question the specificity of these criteria. We identified 4 biopsy specimens from 3 nondiabetic cases and 1 non–insulin-requiring diabetic case that contained the complete constellation of findings described by Tomaszewski et al.[6] We demonstrate that diabetic mastopathy is not exclusive to females and can affect males. It is manifested by solitary or synchronous bilateral masses, as well as nonpalpable lesions, with a propensity for the subareola. Recurrences are not uncommon and occurred in 32% of cases in our series. Recurrences can be ipsilateral, bilateral, or contralateral on repeated occasions.

From the [1]Division of Anatomic Pathology, Vanderbilt University Medical Center, Nashville, TN; the [2]Department of Anatomic and Cellular Pathology, Prince of Wales Hospital, Chinese University of Hong Kong; and [3]The Polyclinic, Seattle, WA.

Address reprint requests to Dr Ely: Dept of Pathology, Division of Anatomic Pathology, Vanderbilt University Medical Center, Nashville, TN 37232.

References

1. Soler NG, Khardori R. Fibrous disease of the breast, thyroiditis and cheiroarthropathy in type I diabetes mellitus. *Lancet*. 1984;1:193-195.
2. Byrd BF, Hartman WH, Graham LS, et al. Mastopathy in insulin-dependent diabetics. *Ann Surg*. 1987;205:529-532.
3. Lammie GA, Borrow LG, Staunton MDM, et al. Sclerosing lymphocytic lobulitis of the breast: evidence for an autoimmune pathogenesis. *Histopathology*. 1991;19:13-20.
4. Schwartz IS, Strauchen JA. Lymphocytic mastopathy: an autoimmune disease of the breast? *Am J Clin Pathol*. 1990;93:725-730.
5. Ashton MA, Lefkowitz M, Tavassoli FA. Epithelioid stromal cells in lymphocytic mastitis: source of confusion with invasive carcinoma. *Mod Pathol*. 1994;7:49-54.
6. Tomaszewski JE, Brooks JS, Hicks D, et al. Diabetic mastopathy: a distinctive clinicopathologic entity. *Hum Pathol*. 1992;23:780-786.
7. Seidman JD, Schnaper LA, Phillips LE. Mastopathy in insulin-requiring diabetes mellitus. *Hum Pathol*. 1994;25:819-824.
8. Bayer U, Horn LC, Schultz HG. Bilateral, tumorlike diabetic mastopathy: progression and regression of the disease during 5-year follow up. *Eur J Radiol*. 1998;26:248-253.
9. Foschini MP, Cavazza A, Pinto IM, et al. Diabetic fibrous mastopathy: report of two cases. *Virchows Arch A Pathol Anat Histopathol*. 1990;417:529-532.
10. Morgan MC, Weaver MG, Crowe JP, et al. Diabetic mastopathy: a clinicopathologic study in palpable and nonpalpable breast lesions. *Mod Pathol*. 1995;8:349-354.
11. Rollins SD. Fine-needle aspiration cytology of diabetic fibrous mastopathy. *Diagn Cytopathol*. 1993;9:687-690.
12. O'Toole EA, Kennedy U, Nolan JJ, et al. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. *Br J Dermatol*. 1999;140:283-286.
13. Abrahamson DR. Recent studies on the structure and pathology of basement membranes. *J Pathol*. 1986;149:257-278.
14. Sternberg M, Cohen-Fortere L, Peyroux J. Connective tissue in diabetes mellitus: biochemical alterations of the extracellular matrix with special reference to proteoglycans, collagens and basement membranes. *Diabetes Metab*. 1985;11:27-50.
15. Bottazzo GF, Pujolo-Borrell R, Hanafusa T, et al. Role of aberrant HLA-DR expression and antigen presentation in the induction of endocrine autoimmunity. *Lancet*. 1983;2:1115-1119.

HOLOGIC®

First and Only FDA Cleared
Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

genius™
DIGITAL DIAGNOSTICS