“Diabetic Mastopathy,” or Sclerosing Lymphocytic Lobulitis, Is Strongly Associated With Type 1 Diabetes

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OBJECTIVE — To demonstrate the strong association of diabetic mastopathy or sclerosing lymphocytic lobulitis with type 1 diabetes mellitus by studying appropriate control groups and to describe risk factors and natural history of the disorder.

RESEARCH DESIGN AND METHODS — This was a retrospective cross-sectional study of four groups of patients conducted at a setting tertiary care medical center. We examined benign breast biopsies (investigator masked to identity) from age-matched patients with types 1 and 2 diabetes, autoimmune thyroid disease, or none of the above disorders for sclerosing lymphocytic lobulitis. Several risk factors proposed for the disorder (age at diagnosis of benign breast disease, duration of diabetes, age at onset of diabetes, prevalence of retinopathy, neuropathy, nephropathy and cheiroarthropathy, glycemic control, parity, oral contraceptive use, menopausal status, or number of breast biopsies) were evaluated, and patients were contacted to describe the natural history of the disorder.

RESULTS — Sclerosing lymphocytic lobulitis was identified in 69.7% of the subjects with type 1 diabetes and 1.8% of those with autoimmune thyroid disease diagnosed with benign breast disease at surgery. It did not occur in patients with type 2 diabetes with or without insulin treatment or in control subjects. Only retinopathy and peripheral neuropathy were associated with sclerosing lymphocytic lobulitis. Breast carcinoma or lymphoma did not occur subsequently in any type 1 diabetes patient with or without sclerosing lymphocytic lobulitis.

CONCLUSIONS — Sclerosing lymphocytic lobulitis is strongly associated with type 1 diabetes. Retinopathy and neuropathy are associated with the disorder. The risk of malignancy is not increased.

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Diabetes is characterized by the occurrence of acute and chronic complications. Common chronic complications include nephropathy, retinopathy, neuropathy, and macrovascular disease. An inadequately studied complication affecting the breasts of women with diabetes has been termed “diabetic mastopathy” (1–14).

Several case reports and case series have described a syndrome of multiple breast lumps and dense mammographic pattern in patients mostly with—but sometimes without—diabetes (1–10). Biopsies were undertaken in such patients for a dominant breast lump or multiple nodules difficult to evaluate by mammography. The microscopic evaluation revealed keloid-like fibrosis of the mammary stroma with or without lymphocytic lobulitis. Reports documenting these pathological changes with or without diabetes have termed the disorder diabetic mastopathy, sclerosing lymphocytic lobulitis of the breast, fibrous mastopathy, or lymphocytic mastopathy (1–14).

There are several shortcomings in the published literature regarding sclerosing lymphocytic lobulitis. Previous studies have used the terms “insulin-dependent” and “insulin-treated” interchangeably when describing patients with the disorder (8–10). Thus, the relative frequencies of this disorder in types 1 and 2 diabetes have not been clearly defined, and the relationship of insulin injections to the disorder has not been evaluated. Appropriate control groups have not been studied in a blinded manner to establish the strong association of this disorder with type 1 diabetes (8–10). Patients with breast cancer (in whom breast parenchyma adjacent to the tumor may contain an inflammatory infiltrate) have been included in previous studies (10). The presence of microvascular disease, neuropathy, and cheiroarthropathy has been described as risk factors for the disorder without a control group and, furthermore, no previous study has defined the criteria for the presence of each of these complications (1,8–10). Finally, the role of hormonal factors (such as oral contraceptive use) as a risk factor for the disorder, the need for recurrent biopsies, and whether predisposition for malignant change exists has not been reported.

We studied patients with type 1 diabetes, type 2 diabetes, or autoimmune thyroid disease and patients without any of these disorders who, after surgery, had been diagnosed to have benign breast disease. We also addressed the question of the relationship of insulin administration to the disorder by studying patients with type 2 diabetes treated with and without insulin. We examined the association of several risk factors for the development of this disorder in patients with type 1 diabetes, and we documented the natural history of the disorder from the medical records and by patient contact.

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Abbreviations: IRB, institutional review board; RDN5, Rochester Diabetic Neuropathy Study.

A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.
Sclerosing lymphocytic lobulitis type 1 diabetes

RESEARCH DESIGN AND METHODS

Patient selection
Pilot study. To determine the prevalence of the disorder in diabetes, we studied patients enrolled in the Rochester Diabetic Neuropathy Study (RDNS). Briefly, this study addresses the natural history and risk factors for neuropathy in patients with types 1 and 2 diabetes in comparison with age- and sex-matched control subjects from the same county (15). We reviewed their records for breast surgery/biopsy. Of 68 and 92 women, respectively, with types 1 and 2 diabetes enrolled in the study, 5 with type 1 diabetes and 17 with type 2 diabetes were found to have surgically proven benign breast disease. Although characteristic changes of sclerosing lymphocytic lobulitis were present in four of five patients with type 1 diabetes (prevalence 80%), none of the 17 (0%) with type 2 diabetes showed these changes. The study was approved by the institutional review board (IRB).

Description of the study groups
Group 1. All patients diagnosed with benign breast disease from 1986 through 1995 were identified from the pathology records. We identified patients who underwent breast surgery by a computer search of the Mayo Medical Records. Patients with type 1 diabetes were identified by cross-indexing the search terms “juvenile diabetes” and “insulin-dependent diabetes mellitus” and benign breast disease. We retrieved a list of 153 patients. Medical records of all patients diagnosed as juvenile or insulin-dependent diabetes mellitus during the clinical encounter were reviewed because we expected the disorder to be rare. Patients were classified as type 1 or 2 diabetes based on standard clinical criteria (16). Patients were excluded if carcinoma was present in this or previous specimens (n = 4). This was done because carcinoma in the breast is frequently associated with lymphocytic infiltration independent of any associated condition. Patients with clinical type 2 diabetes misclassified as “insulin-dependent diabetes” were excluded (n = 120). Five patients were excluded because of the presence of autoimmune thyroid disease. Therefore, 24 patients were identified in group 1.

Group 2. We identified patients with type 2 diabetes by using the search terms “diabetes mellitus” and “benign breast disease” (n = 1,058). Patients who appeared in more than one list and those with carcinoma were excluded (n = 29 for type 1 diabetes; n = 533 for carcinoma; and n = 103 for coexistent thyroid disease). Patients were age-matched to group 1. The most closely matched records were reviewed to obtain 55 patients satisfying selection criteria of the presence of type 2 diabetes and the absence of prior breast carcinoma and autoimmune thyroid disease. We retrieved details of treatment of the diabetes at breast surgery from the medical records.

Group 3. Patients with autoimmune thyroid disease were identified by cross-indexing the terms “thyroid disease” and “benign breast disease” (n = 1,807). Patients who appeared in more than one list were excluded from further study to eliminate the confounding effects of multiple diseases (n = 5 for type 1 diabetes; n = 103 for type 2 diabetes; and n = 848 for carcinoma). Patients were age-matched to group 1. Autoimmune thyroid disease was based on a history of hypothyroidism, either in the absence of a previous thyroidectomy or with antimicrosomal antibodies; Graves’ disease; or euthyroid goiter with antimicrosomal antibodies.

Altogether, 81 medical records were reviewed to select 55 patients who satisfied selection criteria; 26 were excluded because of carcinoma or other types of thyroid disease. We chose patients with autoimmune thyroid disease because we hypothesized that sclerosing lymphocytic lobulitis is autoimmune in pathogenesis and therefore might be expected to occur in association with the most common organ-specific autoimmune disorder.

Group 4. The pathology database identified 8,947 patients diagnosed with surgically proven benign breast disease between 1986 and 1995. We excluded 1,350 patients (n = 851 for diabetes and n = 499 for thyroid). From 7,597 patients, the most closely matched records were reviewed to obtain 55 patients satisfying selection criteria.

Pathology
All specimens were examined by frozen section before formalin fixation and paraffin embedding. Hematoxylin and eosin–stained paraffin sections (1–6 slides per biopsy) were evaluated in a blinded manner by two investigators (T.B.C and C.R) for the morphological features of sclerosing lymphocytic lobulitis, as previously described (8,10,11). Immunophenotyping of lymphocytes was carried out with antibodies against T-cell (CD3) and B-cell (L26/CD20) markers on formalin-fixed paraffin-embedded tissue.

Risk factors for sclerosing lymphocytic lobulitis
To assess risk factors for the development of the disorder, all patients with type 1 diabetes and benign breast disease (n = 33) identified in the course of our clinical investigation were studied (including 24 in group 1, 5 with type 1 diabetes and auto-immune thyroid disease, and 4 from the RDNS who were not identified by the computer search because the diagnosis was made before 1986). The medical records were reviewed for age, duration of diabetes, glycemic control, presence of microvascular complications, neuroopathy, diabetic hand syndrome or cheiroarthropathy, and natural history of the disorder. All glycosylated hemoglobin concentrations available for each patient before the development of the disorder were retrieved from the record, but only the concentrations within 3 months from the date of biopsy are shown and used in analysis. Diabetic retinopathy was defined on the basis of either dilated eye examination carried out by an ophthalmologist or a history of photocoagulation for proliferative retinopathy. Diabetic neuropathy was defined as a chronic increase in serum creatinine above normal or the presence of gross proteinuria (>500 mg/24 h) in the absence of other causes. Clinical examination revealing the presence of neurological deficits characteristic of peripheral neuropathy in the absence of other causes for the changes was considered as diabetic neuropathy. Cheiroarthropathy was diagnosed on the basis of limitation of hand and finger movements (17). Number of pregnancies, oral contraceptive use, menopause, and hormone replacement therapy were ascertained for each patient with type 1 diabetes by patient contact using an IRB-approved structured questionnaire.

Follow-up of patients with type 1 diabetes and benign breast disease
All patients with type 1 diabetes and benign breast disease were contacted by telephone or mail to ascertain the number
of biopsies and subsequent diagnosis of breast malignancy, if any.

**Statistical analysis**
Patients matched for age to group 1 were identified from each of the other three groups using SAS software. Based on the results from the RDNS, we planned to study 55 patients from each group under study. This would give us >95% power to detect a difference between prevalence rates of <5 and 50% in the non–type 1 diabetic patient groups and the type 1 diabetic patient group, respectively.

Wilcoxon rank-sum tests were used to analyze data that were not normally distributed. A two-sample t test was used to analyze normally distributed data. Fisher’s exact test was used for categorical data. Logistic regression was performed for each proposed risk factor to determine whether the risk factor was significantly associated with sclerosing lymphocytic lobulitis in type 1 diabetic subjects. χ² tests were used to determine whether the association of each risk factor to sclerosing lymphocytic lobulitis was statistically significant. SAS software was used to perform all analyses, and all statistical tests were performed at the 0.05 level of significance.

**RESULTS**

**Pathology**

**Group 1.** A total of 24 patients were studied (mean age 41.3 ± 9.2 years). The histopathologic features of diabetic mastopathy were identified in biopsy specimens from 17 (69%) of 24 patients. Gross examination typically demonstrated ill-defined firm breast tissue, and low-power magnification demonstrated histological evidence of lymphocytic lobulitis and keloidal fibrosis. The majority of the lobular units were atrophic and clearly defined at low-power magnification by the lymphocytic infiltrate, which was sharply confined to the lobules and specialized mammary stroma (Fig. 1A and B). High-power magnification demonstrated that the lymphocytic infiltrate was composed of mature small lymphocytes. In most instances, all of the lobules present in the biopsy specimen demonstrated some degree of lymphocytic infiltration, but the density varied from lobule to lobule. Perivascular lymphocytic infiltrate was present in each of the specimens (Fig. 1C). The interlobular stroma revealed scattered fibroblasts with moderately large, ovoid nuclei and abundant cytoplasm (“epithelioid fibroblasts”) in a background of dense keloidal fibrosis (Fig. 1D). The number of epithelioid fibroblasts varied between subjects but was generally small. Sequential biopsies from the same patient revealed similar morphological features in each specimen, without any clear pattern of progression. In 10 subjects, analysis of the infiltrating lymphocytes showed a predominance of B-cells (71 ± 14%). When all of the patients with type 1 diabetes and benign breast disease (n = 33) identified in the course of our clinical investigation were studied (see the RESEARCH DESIGN AND METHODS section on risk factors for sclerosing lymphocytic lobulitis for details of how subjects were identified), 23 showed changes consistent with sclerosing lymphocytic lobulitis.

**Groups 2–4.** A total of 55 patients were studied from each group. The median age in group 2 was 48.3 ± 7.9 years (P = 0.014 compared with ages in group 1). Groups 3 and 4 were age-matched to group 1 (mean age 40.8 ± 8.8 and 40.9 ± 8.7 years, respectively). In the autoimmune thyroid disease group, 8 patients showed euthyroid goiter with antithyroid antibodies, 39 had hypothyroidism in the absence of surgery or any other cause, and 8 had Graves’ disease. None of the breast specimens from patients in groups 2 or 4 showed the histopathologic features of sclerosing lymphocytic lobulitis (n = 55 in each group), but one patient in group 3 (autoimmune thyroid disease) showed changes consistent with the disorder. Therefore, the entity was strongly associated with type 1 diabetes (P < 0.001).

**Relationship of insulin treatment to sclerosing lymphocytic lobulitis in diabetes**

We compared the prevalence of the disorder in patients with type 1 diabetes with those patients with type 2 diabetes who were treated with insulin to evaluate whether insulin treatment was associated with sclerosing lymphocytic lobulitis. The entity did not occur in any of the 17...
patients treated with insulin in the type 2 diabetes group, suggesting that insulin treatment is not associated with the disorder ($P < 0.001$). However, the type 2 diabetes group was older than group 1 ($47.3 \pm 7.2$ vs. $41.4 \pm 8.7$ years; $P = 0.019$).

### Clinical presentation of patients with sclerosing lymphocytic lobulitis

The indication for first biopsy was a dominant nodule in 21 of 23 patients with type 1 diabetes and sclerosing lymphocytic lobulitis, 9 of 10 patients with type 1 diabetes without the disorder, and the 1 patient in group 3. The remaining three patients with type 1 diabetes underwent biopsies because of multiple palpable breast nodules without a dominant nodule and dense breast tissue that could not be satisfactorily evaluated by imaging.

### Clinical characteristics of patients with sclerosing lymphocytic lobulitis

Age of the patients, duration of diabetes, age at onset of diabetes, glycosylated hemoglobin concentration, frequency of complications (nephropathy and cheiroarthropathy), and number of pregnancies before biopsy did not differ between the two groups (Table 1). Patients with sclerosing lymphocytic lobulitis showed significantly higher prevalence of neuropathy and retinopathy (Table 1).

### Follow-up of patients with type 1 diabetes and benign breast disease

We attempted to contact all patients with type 1 diabetes and benign breast disease in our study. Altogether, 16 patients with sclerosing lymphocytic lobulitis and 6 without the disorder responded to our questionnaire. Four patients with the disorder and two without did not return the questionnaire. Patients who did not return the questionnaire received follow-up at our medical center (median 3.9 vs. 4.5 years). Three patients with sclerosing lymphocytic lobulitis and two without the disorder in the type 1 diabetes group are deceased (median 10.8 years in the former vs. 5.4 in the latter). The deceased patients had also returned to Mayo Clinic for follow-up until close to their demise.

More patients with sclerosing lymphocytic lobulitis underwent repeat biopsies over a longer period of follow-up, but the difference was not statistically significant (Table 1). None of the patients developed breast carcinoma or lymphoma during the follow-up period (232.5 patient years for patients with type 1 diabetes and sclerosing lymphocytic lobulitis, 70.3 for those without the disorder) (Table 1).

### Table—Clinical characteristics of patients with type 1 diabetes and histopathologically proven benign breast disease

<table>
<thead>
<tr>
<th></th>
<th>SLL</th>
<th>No SLL</th>
<th>$P$</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at breast biopsy</td>
<td>Median</td>
<td>41.0</td>
<td>45.5</td>
<td>0.0967</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>33.0–45.0</td>
<td>37.8–50.0</td>
<td>0.835–1.015</td>
</tr>
<tr>
<td>Age at diagnosis of diabetes</td>
<td>Median</td>
<td>12.0</td>
<td>18.0</td>
<td>0.0759</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>10.0–17.0</td>
<td>11.8–28.8</td>
<td>0.839–1.009</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>Median</td>
<td>26.0</td>
<td>29.0</td>
<td>0.8440</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>19.0–30.0</td>
<td>16.3–33.3</td>
<td>0.928–1.095</td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>Median</td>
<td>11.3</td>
<td>9.0</td>
<td>0.2007</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>8.3–13.3</td>
<td>8.7–10.2</td>
<td>0.894–1.702</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>20 (91)</td>
<td>6 (60)</td>
<td>0.0475</td>
<td>7.000 (1.021–47.97)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>19 (86)</td>
<td>5 (50)</td>
<td>0.0157</td>
<td>10.50 (1.56–70.76)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>11 (50)</td>
<td>4 (40)</td>
<td>0.6787</td>
<td>1.375 (0.305–6.203)</td>
</tr>
<tr>
<td>Cheiroarthropathy</td>
<td>9 (41)</td>
<td>3 (30)</td>
<td>0.3458</td>
<td>2.139 (0.440–10.39)</td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>Median</td>
<td>1.00</td>
<td>1.00</td>
<td>0.2644</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>(1.0–2.0)</td>
<td>(1.0–1.0)</td>
<td>(0.600–6.443)</td>
</tr>
<tr>
<td>Parity</td>
<td>Median</td>
<td>1.00</td>
<td>2.50</td>
<td>0.3471</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>(0–3.0)</td>
<td>(0–4.3)</td>
<td>(0.546–1.237)</td>
</tr>
<tr>
<td>OCP use</td>
<td>6 (26.1)</td>
<td>4 (40)</td>
<td>0.4693</td>
<td>1.794 (0.368–8.746)</td>
</tr>
<tr>
<td>Menopause</td>
<td>10 (43.5)</td>
<td>3 (30)</td>
<td>0.4273</td>
<td>0.529 (0.110–2.346)</td>
</tr>
<tr>
<td>Estrogen use in postmenopausal</td>
<td>3 (50)</td>
<td>1 (25)</td>
<td>&gt;0.05</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>Median</td>
<td>9.9</td>
<td>6.2</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Interquartile range (25–75%)</td>
<td>(6.8–13.3)</td>
<td>(3.1–10)</td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are $n$ (%) or median (interquartile range) unless otherwise indicated. OCP, oral contraceptives; SLL, sclerosing lymphocytic lobulitis.
CONCLUSIONS — We studied benign breast biopsies in patients with types 1 and 2 diabetes, autoimmune thyroid disease, and benign breast disease without any of the above-mentioned disorders. Sclerosing lymphocytic lobulitis was present only in 23 patients with type 1 diabetes and 1 patient with autoimmune thyroid disease. There was no difference in multiple risk factors evaluated between those type 1 diabetic patients with and without sclerosing lymphocytic lobulitis. The prevalence of neuropathy and retinopathy was significantly higher in the presence of the pathological disorder. Malignant change did not occur in any patient with type 1 diabetes on follow-up.

We have shown the strong association of this disorder with type 1 diabetes. Our study was the first to evaluate benign breast tissue in a blinded manner from age-matched patients with types 1 and 2 diabetes, patients with a highly prevalent organ-specific autoimmune disorder such as autoimmune thyroid disease, and control subjects. Patients described before the report of Tomaszewski et al. (8) did not always fulfill the criteria that were described by the investigators and that have since been accepted for the diagnosis of the disorder. Tomaszewski et al. (8) studied 8 patients with long-standing diabetes (6 patients with type 1 diabetes and 2 with type 2 diabetes) and breast masses and 36 patients with benign breast disease who were not diabetic or had diabetes of short duration. Seidman et al. (9) studied breast tissue from 21 diabetic patients, 30 age-matched control subjects, and 6 patients with abnormal thyroid function (cause of thyroid disease not described). Patients with diabetes were not classified as type 1 and type 2 in the study. Morgan et al. (10) studied biopsies from two groups of 20 patients with and without diabetes. Patients with breast cancer were not excluded from the study groups. The terms type 1 and 2 diabetes were not clearly defined in the study.

We evaluated several risk factors for the development of sclerosing lymphocytic lobulitis. To our knowledge, ours is the first study to evaluate the relationship between development of the disorder and age at diagnosis of the breast disorder, age at onset of diabetes, and duration of diabetes. We did not find any relationship between these variables and the disorder. Previous studies described the association of poor glycemic control and sclerosing lymphocytic lobulitis, but without a control group. Our data, complete with the appropriate control group, have demonstrated the lack of such an association. Prior studies have reported the association of microvascular complications, neuropathy, and cheiroarthropathy in patients with sclerosing lymphocytic lobulitis (1,8–10). Limitations of previous studies include a lack of definition of criteria for each complication and a lack of control groups. Our study is the first to evaluate the prevalence of each association in patients with type 1 diabetes with and without sclerosing lymphocytic lobulitis. Except for neuropathy and retinopathy, the prevalence of each of these variables in the presence or absence of the disorder was not significantly different. Tissue affected by cheiroarthropathy does not show lymphocytic infiltration (17) and therefore is probably mediated by separate pathogenic mechanisms. Ours is also the first report to study the relationship between various hormonal factors and sclerosing lymphocytic lobulitis. We did not find any association between the number of pregnancies, oral contraceptive use, and menopause on the one hand and the development of sclerosing lymphocytic lobulitis on the other.

The current study makes several more points about sclerosing lymphocytic lobulitis. First, although a strong association of the entity with type 1 diabetes is documented, others have shown that the histopathologic features of this entity are recognized in the absence of diabetes. Such studies have been case series from pathology archives. Our data, complete with appropriate control subjects, provide evidence that the disorder is strongly associated with type 1 diabetes. Second, insulin treatment is not related to the prevalence of sclerosing lymphocytic lobulitis, as speculated in a previous study (9). Third, although insulin affected by immune-mediated mechanisms may show an increased incidence of tumors such as carcinoma, lymphoma, or both (e.g., idiopathic ulcerative colitis, celiac sprue), sclerosing lymphocytic lobulitis was not associated with an increased risk of malignancy on follow-up. Finally, without the presence of a control group, sclerosing lymphocytic lobulitis has been described to result in the need for multiple biopsies. Although our numbers are small, we found that multiple biopsies were not common when compared with type 1 diabetes patients who had other types of benign breast disease.

Our study has several limitations. The points made by this study apply only to women with type 1 diabetes who have undergone biopsy or surgery for a suspicious breast lump or lesion and were subsequently found to have benign breast disease. We do not know the prevalence of sclerosing lymphocytic lobulitis overall in women with type 1 diabetes. Referral bias is a concern in a retrospective study conducted at a large tertiary care center such as the Mayo Clinic. Prevalence rates in the patient population are often higher than those in the general population because of the large number of referral patients seen at a large tertiary care center. The observed prevalence rates in our study are 0%, 1.8%, and 0%, respectively, for groups 2, 3, and 4. The prevalence in the type 1 diabetes patients who had a breast biopsy and were subsequently found to have benign breast disease is not greater than that observed in the RDNS (a population-based study). Hence, we are reassured that referral bias did not have a significant influence on our inferences. Groups 3 and 4 were age-matched to group 1. However, because the onset of type 2 diabetes occurred much later in life compared with that of type 1 diabetes, the type 2 diabetic patients in our study were older. Our conclusion about glycemic control and the lack of association with sclerosing lymphocytic lobulitis is limited by a lack of availability of longitudinal details regarding glycemic control. It should be noted that we restricted our study to women. Sclerosing lymphocytic lobulitis may occur in men, and to date five patients with unequivocal sclerosing lymphocytic lobulitis have been described; all of these patients also had type 1 diabetes (19–21). However, surgery in men represents <5% of all such surgeries at our institution (428 of 8,947 with surgically proven benign breast disease). Based on our study in women, the number of women with type 1 diabetes who were found to have pathologically proven benign breast disease was 0.004%. Therefore, we did not have enough power to draw any conclusions by evaluating men.

Previous reports and our work have demonstrated the strong association of sclerosing lymphocytic lobulitis with type 1 diabetes and have shown that it is an immune-mediated disorder. Subsets of lymphocytes infiltrating involved tissues
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in autoimmune disorders may vary depending on the type of immune-mediated disorder studied and the time point in the natural history of the disorder at which the tissue was sampled (18). Our observation of B-cell predominance in involved tissue confirms previous reports (8,11). At this stage, no conclusion can be drawn regarding the category of immune-mediated disorder that sclerosing lymphocytic lobulitis represents or the immunopathogenesis of the disorder.

Data presented in our study has the following implications for women with type 1 diabetes undergoing biopsies of suspicious breast lesions. First, a first biopsy cannot be avoided in such patients. For the present, the management should not change unless newer methods of imaging, such as magnetic resonance imaging and digital mammography, are compared in a masked trial with more prevalent methods, such as mammography and ultrasound. Second, if the lesion is benign, up to two-thirds of such lesions may be a specific entity termed “sclerosing lymphocytic lobulitis.” Third, poor glycemic control may not exacerbate the disorder. Fourth, the disorder is not associated with a more frequent need for future biopsies. Finally, the risk of breast malignancy is not increased, although longer follow-up is required to prove this point.

In conclusion, sclerosing lymphocytic lobulitis occurs predominantly in type 1 diabetes. Of the multiple risk factors studied, only neuropathy and retinopathy were associated with the disorder. The risk of neoplasia in breast tissue affected by the disorder is not increased.

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References