Diabetic Mastopathy

A Report of 5 Cases and a Review of the Literature

Patricia M. Camuto, MD; Eleonore Zetrenne, MD; Teresa Ponn, MD

Background: Diabetic mastopathy is an unusual fibro-inflammatory breast lesion that characteristically presents in premenopausal women with long-standing type 1 diabetes mellitus with multiple microvascular complications. The pathogenesis of this condition is believed to involve an autoimmune reaction to the accumulation of abnormal matrix induced by hyperglycemia. Clinico-pathologic features include the development of dense keloidlike breast masses that are often recurrent or bilateral or both. Clinical distinction from a malignancy can be difficult. However, the benign nature of this lesion is easily recognized on histologic examination, and it is not associated with an increased incidence of epithelial or stromal neoplasia.

Hypothesis: A constellation of histopathologic and clinical features is necessary to make the diagnosis of diabetic mastopathy. Unnecessary surgery can be avoided in the clinical follow-up of patients with multiple, bilateral, and recurrent lesions.

Design: Case series.

Patients and Methods: Between December 1993 and December 1998, 5 premenopausal women with type 1 diabetes mellitus of 18 to 23 years’ duration presented with nontender, palpable, firm-to-hard breast masses. To date, progression of the tumorlike proliferations has been bilateral and recurrent in 2 patients, bilateral in a third patient, and recurrent in a fourth. The fifth patient has developed neither bilateral nor recurrent lesions. Imaging studies did not in any patient demonstrate a focal lesion. All lesions were treated by either excisional (4 patients) or core (1 patient) biopsy. The resected specimens were examined histopathologically.

Results: Gross examination of the specimens showed firm masses with homogeneous tannish-white cut surfaces. They measured between 3.0 and 6.0 cm in maximum diameter. Microscopic examination showed keloidal fibrosis with ductitis, lobulitis, and vasculitis. The clinical profile in combination with these pathologic features is characteristic of diabetic mastopathy.

Conclusions: Physicians should be aware of the association of long-standing diabetes mellitus with the development of benign fibroinflammatory breast lesions when managing these in premenopausal women. We outline the constellation of findings on clinical examination, medical history, imaging studies, and histopathologic examination that are required to make the diagnosis of diabetic mastopathy. Although these breast masses may be recurrent, they are not premalignant. In the appropriate setting, the diagnosis can be made by core biopsy, avoiding unnecessary surgeries in patients with multiple, bilateral, or recurrent lesions.


Various medical conditions are associated with benign breast diseases, for which physicians caring for these patients should maintain a high index of suspicion. An uncommon mastopathy has been identified in association with diabetes mellitus that can simulate a malignant neoplasm on physical examination. Diabetic mastopathy, or diabetic fibrous breast disease, was first described by Soler and Khadori in 1984 as a dense fibrous stromal proliferation that occurred in women with long-standing type 1 diabetes mellitus and multiple microvascular complications. Since that time, further studies have elucidated the histopathologic features of this unusual fibroinflammatory lesion that represents less than 1% of benign breast lesions. We describe the clinicopathologic features of 5 cases of diabetic mastopathy.

Results

The 5 women ranged in age at onset of the first breast mass from 30 to 36 years (mean, 34 years) (Table 1). At initial presentation, all patients had had type 1 diabetes...
PATIENTS AND METHODS

Between December 1993 and December 1998, 5 women with type 1 diabetes mellitus presented to the general surgical practice of one of us (T.P.). Their clinical files were reviewed for the type, therapy, and age at onset of diabetes; history of other endocrine abnormalities; age at onset of first breast lesion; findings on physical examination of the breast mass; results of imaging studies, including mammography and ultrasonography; and intraoperative findings.

Nine excisional biopsies and 2 fine-needle aspirations were performed on 4 of 5 patients. The fifth patient underwent 2 core biopsies and 1 fine-needle aspiration. Gross descriptions of all specimens were reviewed. Histologic examination of all slides from the biopsies and aspirations were interpreted by one of us (P.M.C.).

Table 1. Summary of Clinical Features

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Age at onset of DM, y</td>
<td>15</td>
<td>14</td>
<td>12</td>
<td>12</td>
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<tr>
<td>DM complications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Other endocrine disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Age at onset of first breast mass, y</td>
<td>34</td>
<td>36</td>
<td>35</td>
<td>30</td>
<td>35</td>
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<tr>
<td>Duration of DM, y</td>
<td>19</td>
<td>22</td>
<td>23</td>
<td>18</td>
<td>20</td>
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<tr>
<td>Bilateral</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>

*DM indicates diabetes mellitus.

mellitus for 18 to 23 years (mean, 20.4 years), and all had been receiving long-term insulin therapy. All but 1 had complications secondary to diabetes: 3 patients had retinopathy, 1 of whom also had neuropathy, and the fourth experienced renal failure, hypertension, and a previous stroke. Only 1 patient had a secondary endocrine disease, hypothyroidism of unknown etiology.

Physical examination of the patients revealed non-tender, immobile, localized irregular areas in 1 or both breasts that were firm, coarse, and frequently flat. They were neither discrete nor round and were of a different texture from the remainder of the breast. Axillary adenopathy was not found in any patient, and none reported a history of trauma to the area.

All 5 patients underwent mammography and ultrasonography. In all cases, both imaging studies failed to demonstrate any focal lesion that could account for the palpable abnormality. Mammograms showed dense fibroglandular tissue without focal mass or distortion. Similarly, ultrasonograms failed to show any cystic or solid mass. At surgery, the lesions were found to be grossly benign but clearly different from the surrounding breast tissue.

On gross examination, the masses were firm with homogeneous tannish-white cut surfaces. The specimens ranged from 3.0 to 6.0 cm in maximum diameter, including the core biopsy specimen, which was estimated to be about 3 cm. Microscopic examination of all specimens showed dense keloidlike fibrosis associated with perivascular, periductal, and perilobular lymphocytic infiltrates (Figure 1 and Figure 2). Epithelioid fibroblasts were found in 1 case (Figure 2, inset). In all cases, no cystic or hyperplastic changes were noted. The fine-needle aspiration specimens proved insufficient for diagnosis.

Patients were followed up for 1 to 6 years (mean, 3.4 years). The histories showed bilateral lesions in 3 patients, 1 at the time of initial presentation and 2 at 7 months and 3 years, after the first biopsy. Recurrence occurred in 3 cases, 2 of which were also bilateral. One recurred after 1 year with 3 masses in the same location. There were multiple bilateral recurrences in another case 11 months after initial biopsy in the left breast, 4 months after initial biopsy in the right breast, and 13 months after the second biopsies in both breasts. During this time, the masses increased in maximum aggregate diameter from 2.5 to 7.0 cm. Microscopically, the lesions showed the same histologic characteristics as those depicted in Figures 1 and 2.
Diabetic mastopathy is an uncommon tumorlike fibrous proliferation of the breast. The diagnosis requires correlation of a specific clinical profile with distinctive pathologic features. Most published reports of diabetic mastopathy have involved premenopausal women with a long history of type 1 diabetes mellitus complicated by diabetic retinopathy, neuropathy, or nephropathy. A summary of the clinical features reported in the literature is given in Table 2. The mean age of patients at diagnosis of the initial breast lesion ranged from 32.2 to 62.0 years, with the duration of diabetes mellitus ranging from 4 to 43 years. The condition has also been observed in patients with type 2 diabetes mellitus who were insulin dependent and in patients with other endocrine disorders, especially thyroid diseases. There have been rare reports of this condition in men.

Clinical findings included single or multiple ill-defined, nontender, palpable, firm-to-hard masses in 1 or both breasts that raised the suspicion of carcinoma. Mammograms usually showed a localized increased density in the glandular pattern, with no distinct masses, spiculation, or calcifications. One researcher, however, reported single cases in which the mammographic findings were suggestive of carcinoma or lymphoma. Findings on ultrasonography of lesions included strong acoustic shadowing posterior to the nodules, which speculatively correlated with the amount of fibrous tissue. However, no discrete solid or cystic masses were identified using either imaging technique.

Histopathologic examination of these lesions has shown firm homogeneous masses ranging in diameter from 2 to 6 cm. Microscopically, they are characterized by keloidal fibrosis and a variable periductal, perlobular, or perivascular lymphocytic infiltration that consists primarily of B cells. These features have been found to be unique to diabetic mastopathy, in contrast to patients with mastitis and fibrosis secondary to another process. In some cases, epithelioid fibroblasts characterized as rounded cells with abundant cytoplasm and oval nuclei embedded in the dense collagen have been described. Fine-needle aspiration of all these lesions usually yields sparse connective tissue elements.

The pathogenesis of diabetic mastopathy is not completely understood and is most likely multifactorial. Many researchers suggest a role for a secondary autoimmune reaction to abnormal extracellular matrix accumulation that is a manifestation of the effects of hyperglycemia on connective tissue. Hyperglycemia induces glycosylation, increased intermolecular cross-linkage, and matrix expansion that is altered in quantity and quality and resistant to degradation. The accumulation of abnormal matrix and advanced glycosylated end products creates a “neoantigen” that triggers a secondary autoimmune reaction, with B-cell proliferation and autoantibody formation. Subsequent macrophage-mediated advanced glycosylation end product removal and cytokine release may act as growth factors and induce additional matrix expansion and proliferation of collagen.

Diabetic mastopathy has not been linked to subsequent development of mammary carcinoma or stromal neoplasia. For lesions that are unilateral, treatment with excisional biopsy is sufficient. However, a summary of the data in the literature shows that approximately 63% of lesions are bilateral or recurrent or both, which was the case in 4 (80%) of our 5 patients during a mean follow-up of 3.4 years. This suggests that the natural history of this condition involves a multicentric field effect of diabetes on mammary tissue. Since recurrences tended to be in the same location and involved more breast tissue than did the preceding lesion, it may be that the mastopathy affects the healing process and that the surgery itself exacerbates the condition.

To properly counsel and manage these patients, surgeons need to be aware of the association of long-standing diabetes mellitus with the development of distinctive fibroinflammatory breast lesions in premenopausal women. In accordance with previously cited recommendations, we suggest that the diagnosis of diabetic mastopathy can be made when the following constellation of findings is met:

1. The patient is a premenopausal woman with long-standing type 1 diabetes mellitus that is usually associated with microvascular complications. The patient may

<table>
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<tr>
<th>Source, y</th>
<th>No. of Cases</th>
<th>DM Complications</th>
<th>Other Endocrine Disease</th>
<th>Age at Onset of First Breast Mass (y, Average)</th>
<th>Duration of DM (y, Average)</th>
<th>Multiple or Bilateral</th>
<th>Recurrent</th>
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<tr>
<td>Soler and Khandori, 1984</td>
<td>12</td>
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<td>32.2</td>
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<td>Byrd et al., 1987</td>
<td>8</td>
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<td>...</td>
<td>33.9</td>
<td>6.0-37.0</td>
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<td>Logan and Hoffman, 1989</td>
<td>36</td>
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<td>...</td>
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<td>13.0</td>
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<td>2</td>
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<td>0</td>
<td>37.0</td>
<td>21.5</td>
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<td>36.0</td>
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<td>Seidman et al., 1994</td>
<td>5</td>
<td>3</td>
<td>...</td>
<td>47.0</td>
<td>&gt;13.0</td>
<td>24</td>
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<td>Puchinotta et al., 1995</td>
<td>3</td>
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<td>1</td>
<td>34.3</td>
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<td>7</td>
<td>...</td>
<td>62.0</td>
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<td>Rode et al., 1998</td>
<td>8</td>
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<td>41.0</td>
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<td>Camuto et al, 2000</td>
<td>5</td>
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<td>1</td>
<td>34.0</td>
<td>20.4</td>
<td>3</td>
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</table>

* DM indicates diabetes mellitus; ellipses, not reported.
or may not have a history of other endocrine or autoimmune diseases.

2. A palpable breast mass is identified on physical examination that is hard, nontender, and clinically suspicious for carcinoma.

3. Mammographic studies show an increased density but do not confirm the presence of a localized mass. Ultrasonography also fails to identify a solid or cystic mass.

4. Excisional or core biopsy shows dense keloidal fibrosis associated with a perivascularex, periductal, or perilobular lymphocytic infiltrate. Epithelioid fibroblasts may or may not be present. Because fine-needle aspiration specimens are characteristically “inadequate for cyto logic diagnosis,” we do not consider it an adequate means to diagnose or to follow up these patients.

A minimum routine annual follow-up of patients with diabetic mastopathy is recommended, as is our practice for all patients with an abnormal finding on breast examination. Diabetic women with a suspicious breast mass or mammogram who do not have pathologic findings consistent with diabetic mastopathy on core biopsy need an excisional biopsy to rule out neoplasm. However, with a high index of suspicion in the proper clinical setting, the diagnosis of diabetic mastopathy can usually be made on core biopsy, with avoidance of unnecessary surgical procedures that may actually exacerbate the condition.

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REFERENCES


ARCHIVES OF INTERNAL MEDICINE

Clinical Outcome and Cost of Hospital vs Home Treatment of Proximal Deep Vein Thrombosis With a Low-Molecular-Weight Heparin: The Vascular Midi-Pyrenees Study

Henri Boccalon, MD; Antoine Elias, MD; Jean-Jacques Chalé, MD; Agnes Cadène, MD; Sylvie Gabriel, MD; for the Vascular Midi-Pyrenees Network Group

Background: Low-molecular-weight heparins have been shown to be effective and safe in the treatment of deep vein thrombosis. To our knowledge, there have been no direct comparisons of such treatment on an outpatient vs an inpatient basis.

Objective: To conduct a randomized, comparative, multicenter trial to evaluate the clinical outcomes and treatment costs of deep vein thrombosis in the outpatient and inpatient settings.

Methods: Two hundred one patients presenting with proximal deep vein thrombosis, without known risk factors for pulmonary embolism or hemorrhagic complications, were randomized to receive a low-molecular-weight heparin at the registered dose followed by an oral anticoagulant for up to 6 months, either in the hospital for the first 10 days followed by treatment at home (n=102) or at home from the outset (n=99). The primary clinical outcome was the incidence of venous thromboembolism recurrence, pulmonary embolism, or major bleeding. The economic analysis was performed from the point of view of the health insurance company. Total costs of the 2 management strategies were calculated to compare the cost consequences during the first 10 days.

Results: No differences in clinical outcome were detectable between the 2 groups. There was no increase in the rates of primary efficacy outcome in the patients treated at home vs in the hospital (3.0% vs 3.9%), while a cost reduction of 56% was demonstrated for outpatient management.

Conclusion: For patients with proximal deep vein thrombosis and no symptoms of pulmonary embolism or increased risk of major bleeding, home treatment using a low-molecular-weight heparin is an effective, safe, and cost-saving strategy. (2000; 160:1769-1773)

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