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Case report

Diabetic fibrous mastopathy

Report of two cases

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Summary. Two cases of a characteristic form of fibrous mastopathy associated with type I diabetes mellitus are described. Well-circumscribed nests of mature lymphocytes in a hyaline stroma are the hallmark of this condition. In one case mastectomy was performed, as the lesion had been interpreted as malignant on frozen section. It appears that this form of "idiopathic mastopathy" deserves wider recognition.

Key words: Type I diabetes mellitus – Fibrous mastopathy

Introduction

The breast had never been included in the range of the complications of diabetes mellitus until the association between insulin-despendent diabetes mellitus (IDDM), fibrous disease of the breast, cheiroarthropathy and autoimmune thyroiditis was described (Soler and Khardori 1984). Breast lesions appear clinically as multiple breast lumps that may simulate neoplastic conditions. Here two cases of IDDM having fibrous nodules of the breast are reported and the differential diagnosis with similar inflammatory and neoplastic conditions of the breast is discussed.

Case reports

Case 1

The patient was a 37-year-old Italian woman (para 1) with normal menstrual cycle who did not breast feed. She had been affected by IDDM since 1960, when she was 9 years old. She has genetic markers of IDDM: A24, A30, B18, Y, Cw5, Cw6, DR3, DRw52. Neither islet cell antibody nor other markers of organ-specific autoimmunity are present. Among non-organ specific autoantibodies (anti-nucleus, -mitocondria, -ribosomes, -microsomes, -smooth muscle), only anti-smooth-muscle antibody was present.

The patient had been treated with conventional intensified insulin therapy (three daily injections; 40 units/day in total) until October 1988. This therapy was not sufficient to control the hyperglycaemia: haemoglobin A_{1C} (HbA_{1C}) 9.3% (normal values 3.4–5.8%), glycaemia 2.49 g/l (normal values 0.80–1.10 g/l), glycosuria 40 g/l. In 1988 the conventional therapy was substituted with continuous subcutaneous insulin infusions by a portable device that administered 35 units/day insulin. Presently HbA_{1C} is 8%, glycaemia 1.39 g/l, glycosuria 2.5 g/l. Since May 1982 marked leukocytosis (23.7×10^9/l) with eosinophilia (42% eosinophils) and high IgE levels (47500 IU/ml; normal values < 122 IU/ml) have been found. Nevertheless no allergic or inflammatory diseases were present. In June 1982 the patient had a brief episode of diffuse myalgia and arthralgia; rheumatoid factor was present. Inguinal and submandibular lymph nodes were enlarged. A biopsy showed reactive inguinal lymph nodes. The patient, treated with anti-inflammatory drugs, showed rapid improvement of the disease. At present, there is no evidence of rheumatoid factor in the serum; the patient enjoys complete joint mobility. Renal lithiasis was diagnosed in May 1983; there was no evidence of diabetic nephropathy. In January 1984 diabetic background retinopathy was diagnosed.

In April 1982 the patient developed an abscess in the right breast which was treated with drainage and local antibiotic therapy. The abscess resolved into a fibrous lump that was surgically excised 9 months later (January 1983). In July 1988 the patient complained of a lump in her left breast. Ultrasonography showed two solid areas: in the upper inner quadrant (UIQ), measuring 5 cm across; and in the inferior outer quadrant (IOQ), measuring 2 cm across. A cytological smear was non-diagnostic. On frozen section the UIQ lump was diagnosed as "multiple foci of in situ lobular carcinoma, focally invasive". A radical mastectomy with axillary lymph node dissection was performed.

Macroscopically the nodule located in the UIQ, removed for frozen section examination, measured 5.2 cm across and was composed of whitish, homogeneous tissue, rubbery in consistency. The removed breast measured $22 \times 10 \times 4$ cm; the nipple was normal. The breast parenchyma contained numerous nodules varying from a few millimetres to 2.3 cm in greatest dimension. The largest nod-

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ule was located in the IOQ and corresponded to the second nodule detected echographically. All the nodules were macroscopically similar to the first one removed for frozen section examination. Ten lymph nodes were found in the axillary fat.

Case 2

The patient is a 42-year-old Portuguese woman who has been affected by IDDM since she was 22 years old (1970). Glycaemia has never been stable in spite of the insulin therapy and diabetic coma has been reported twice. The patient suffers from chronic limited joint mobility and retinopathy. Thyroiditis has never been apparent nor autoantibodies found. When the patient was aged 36 years (1984) she complained of breast tenderness and nipple discharge. One year later (1985), a left breast nodule was removed. In 1986 a second nodule from the left breast was excised. In 1989 the patient developed two lumps in the contralateral breast which were removed, in February and in December respectively.

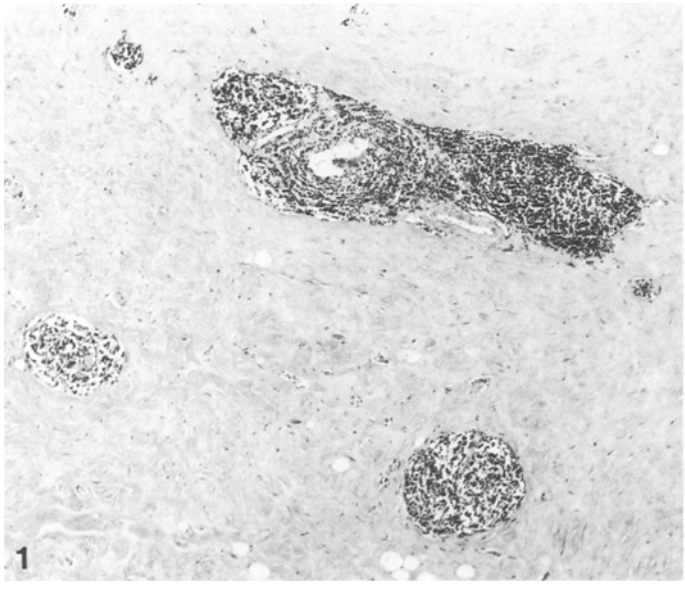
All the nodules had the same macroscopic appearance. They had ill-defined margins and were composed of rubbery, whitish tissue.

Materials and methods

Tissues were fixed in 10% buffered formalin and embedded in paraffin; sections were stained with haematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) prior to and after diastase digestion, Congo red, Masson trichrome, phosphotungstic acid haematoxylin (PTAH), Weigert method for elastic fibres, and May-Grunwald Giemsa. Selected sections were stained immunohistochemically (Hsu et al. 1981a, b) employing the streptavidin-biotin-peroxidase complex (Detek I-hrp, Signal Generating System, Enzo Biochem. Inc., New York). The following antibodies were used: monoclonal anti-pan B (clone CKB5, Dakopatts, Denmark), diluted 1:70 and monoclonal anti-pan T (clone UCHL1, Dakopatts, Denmark), diluted 1:1000. Sections of the right breast lump of case 1, excised in 1983, and all biopsies of case 2 were reviewed.

Results

As the microscopic changes were identical in both cases they will be described together. All breast tissue examined was composed of dense fibrous tissue, where small atrophic ducts and lobules were present. The hallmark of the lesion was composed of lymphoid nests which had well-defined borders neatly outlined by fibrous tissue (Fig. 1), containing scattered fibroblasts. The lymphoid elements were almost entirely represented by mature lymphocytes (Fig. 2), which reacted both with B- and T-lymphoid markers. There was a slight predominance of mature B-lymphocytes. The lymphoid elements were mostly localized around arterioles and capillaries (Fig. 3). A moderate lymphoid infiltrate was also present around ducts and lobules. Rare macrophages were present; no lymphoblasts were seen. The walls of the arterioles were occasionally infiltrated by the lymphoid elements. Basal membranes were thickened around the arterioles and capillaries as well as around the ducts and acini, as revealed by the PAS staining. Atrophic changes were also seen in the ducts and lobules of most of the blocks taken randomly from the breast parenchyma, of case 1, which were macroscopically normal (Fig. 4). All ten axillary lymph nodes examined, in case 1, were reactive. The arterioles and capillaries present in lymph nodes had thick and hyalinized basal lamina. Sections of the breast lump of case 1, excised in 1983, showed areas of dense fibrous tissue, surrounded by normal breast tissue. No lymphoid infiltrate was present. In contrast, in all biopsies reviewed from case 2 there were identical features to those described here.



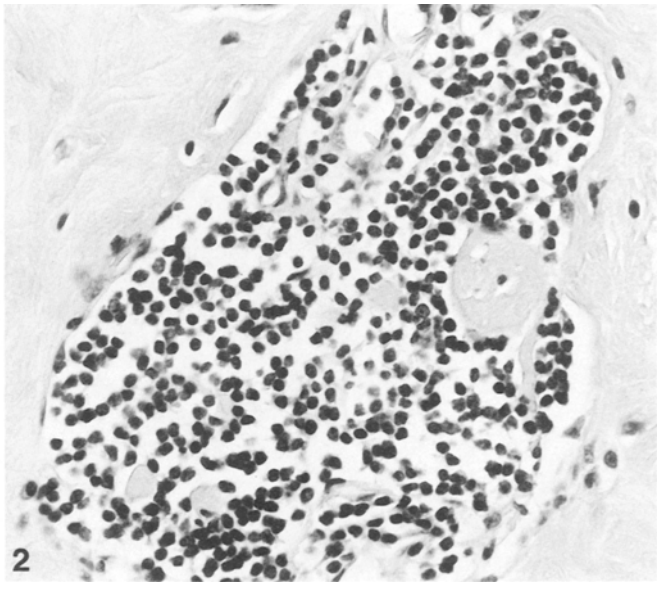
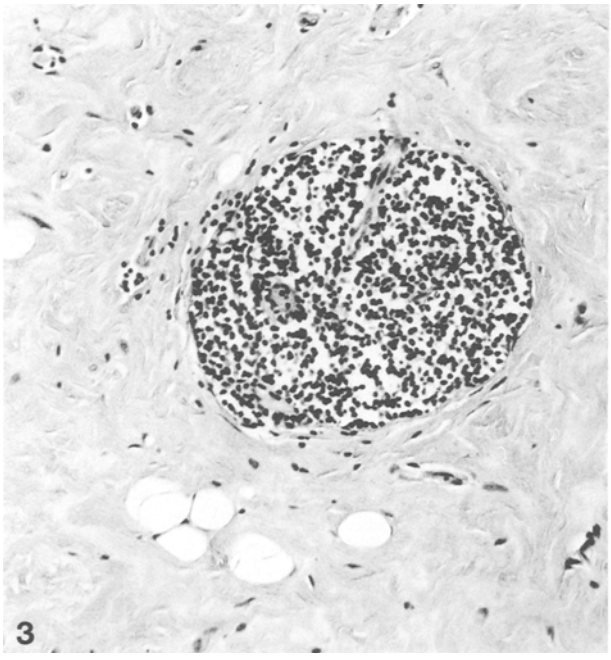


Fig. 1. Case 1: lymphoid nests, neatly outlined by collagenous tissue show a perivascular arrangement. H&E, ×32

Fig. 2. Case 2: the lymphoid nests are constituted mainly by mature lymphocytes. H&E, ×320



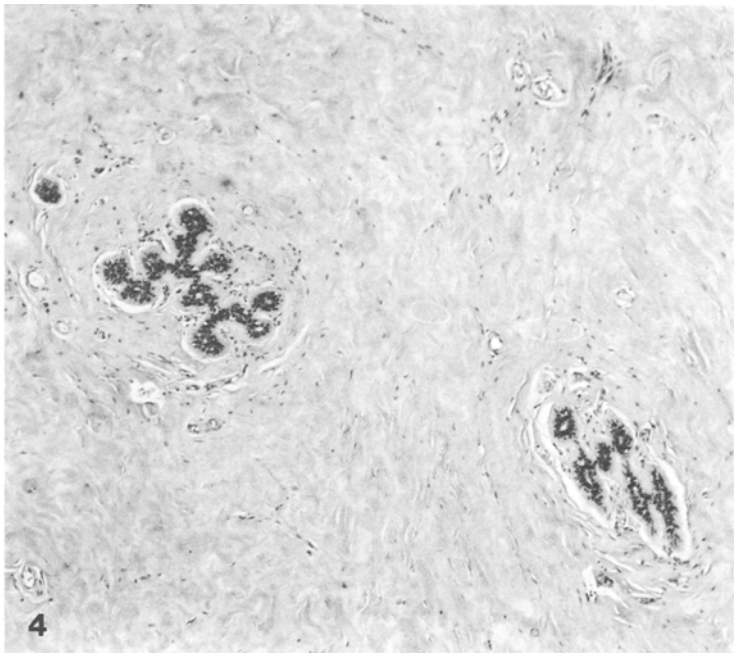


Fig. 3. Case 1: the lymphoid elements surround a small vessel. H&E, ×128

Fig. 4. Case 1: no lobular structures are seen; atrophic ducts are the major constitutents of the breast tissue. H&E, ×51

Discussion

Two cases of fibrous disease of the breast associated with long-standing IDDM are reported. Clinically they were characterized by multiple breast nodules, simulating multifocal carcinoma. Histologically the main distinguishing feature consisted of nests of mature lymphoid elements immersed in dense collagenous tissue. Same collections of lymphocytes were seen in at perivascular position. Basal membranes were thickened around arterioles as well as around ducts and lobules.

Specific forms of arteritides previously described in the breast such as giant cell arteritis (Clement et al. 1987), polyarteritis nodosa and Wegener granulomatosis (Azzopardi 1979) were taken into consideration in the differential diagnosis. At variance with these latter forms of arteritides where the medium-sized arteries are involved, in the present cases only arterioles and capillaries are affected. In addition, no giant cells or necrosis were present in their vascular walls. Specific forms of inflammatory breast conditions (Azzopardi 1979; Rosai 1988) were ruled out on clinical and histological grounds. The patients did not show any clinical or laboratory signs of infection. The diagnosis of granulomatous lobular mastitis (Kessler and Wolloch 1972) was not taken into consideration as in this latter condition the inflammatory infiltrate has a perilobular disposition and is characterized by granulomas with epithelioid histiocytes, giant cells, eosinophils and polymorphonuclear leucocytes (Fletcher et al. 1982). On the contrary in our two cases inflammatory infiltrate was mainly perivascular and almost entirely composed of mature lymphocytes. Case 1 was erroneously interpreted as invasive carcinoma on frozen sections. Lymphocytes may simulate invasive lobular carcinoma (Underwood et al. 1988), but the perivascular disposition of the lymphocytes is distinctive of the present condition. In addition, on permanent sections the lymphocytic nature of the cells is quite apparent. Lymphocytic infiltration may lead to the suspicion of breast lymphoma or pseudolymphoma. In breast lymphomas the bulk of the lesion is composed of an irregularly outlined accumulation of immature lymphocytes which occasionally involve the glandular epithelium (Lamovec and Jancar 1987). In contrast, in the present cases, the lymphocytic infiltrate has sharply defined borders, entirely composed of mature lymphocytes, immersed in dense fibrous tissue and no epithelial involvement is seen. Pseudolymphomas of the breast are characterized by sharply circumscribed clusters of mature lymphocytes with germinal centres, sometimes associated with foci of stromal fibrosis (Lin et al. 1980). In our cases fibrosis was prominent; lymphocytic infiltrate was focal and germinal centres were absent.

The association between fibrous breast lumps and long-standing IDDM was first pointed out by Soler and Khardori (1984), who described 12 out of 88 women (13%), affected by long-standing IDDM and presenting clinically with breast nodules. Since then 16 further cases have been reported (Byrd et al. 1987; Tomaszewski et al. 1990). All the reported cases had the same histological appearance as the present two cases.

Soler and Khardori (1984) argued that fibrous breast lumps might have resulted from connective tissue damage due to persistent hyperglycaemia or autoimmunity.

The possibility of an autoimmune disease was supported by the fact that among their patients 11 out of 12 manifested cheiroarthropathy or Hashimoto's thyroiditis. The hypothesis of an autoimmune disease is favoured also by Tomaszewski et al. (1990), on the basis of histological and immunohistochemical features.

The present patients have no definite signs of autoimmune diseases or definite arthropathic changes and therefore it seems that autoimmune aetiology is not the major cause of this condition. In spite of the accurate and lucid description of Soler and Khardori, this lesion does not appear to be widely recognized, as it is rarely mentioned in the literature (Byrd et al. 1987; Page and Anderson 1987; Tomaszewski et al. 1990). Diabetic fibrous mastopathy may clinically simulate invasive carcinoma of the breast (Byrd et al. 1987). In case 1 the breast was removed as a result of an erroneous interpretation of the lesion at frozen section. Therefore it appears that "diabetic fibrous mastopathy" is a well-defined condition which deserves wider recognition in order to avoid incorrect interpretation.

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Note added in proof

Since the submission of this article eight cases of "Lymphocytic Mastopathy" have been published (Schwartz I.S. and Strauchen J.A.: Lymphocytic Mastopathy, Am. J. Clin. Path. 1990, 93, 725). The histology of these cases is superimposable to those here described. Only one out of eight cases was associated with diabetes. For all an autoimmune condition is proposed.