Breast diseases associated with systemic medical disorders

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Abstract

A wide range of systemic disorders may present as breast lesions, in some cases mimicking primary breast carcinoma and other primary breast diseases clinically and radiologically. The distinction between the manifestation of a systemic medical disorder in the breast and primary breast pathology is clinically important as management and follow-up may defer widely. However, apart from diabetes mellitus-associated breast disease, the manifestation of systemic disorders on breast tissue is rare and the general histopathologist is unlikely to encounter this regularly. This review examines the most common benign breast lesions associated with systemic medical disorders and drugs, including the typical clinical and radiological findings, pathogenesis, and macroscopic and microscopic findings. The specific features and immunohistochemical techniques helpful in differentiating benign disease from carcinoma will be discussed and illustrated using examples from our own practice.

Keywords benign breast disease; Cowden's disease; diabetic mastopathy; IgG4 related disease; systemic medical disorders

Introduction

It is very unusual for a systemic medical disorder (SMD) to present primarily as a breast condition, and a common scenario that confronts the pathologist in this area is being sent a biopsy of a breast lump without a relevant clinical history. The most common SMD associated with breast disease is by far diabetes mellitus. Thereafter, we are in territory that is little travelled and definitely in the 'small print' of the textbooks. In this review we will discuss briefly breast lesions associated with the following conditions: diabetes mellitus; systemic lupus erythematosus; vasculitides; IgG4 related disease; sarcoid and other granulomatous diseases; amyloidosis; Cowden disease and drugs.

Diabetic mastopathy/sclerosing lymphocytic lobulitis

Sclerosing lymphocytic lobulitis is an inflammatory disorder of the breast which shows a strong association with autoimmune diseases, particularly insulin dependent diabetes mellitus. In addition to sclerosing lymphocytic lobulitis, the entity has been recognised under a variety of terms including lymphocytic mastopathy, fibrous mastopathy and diabetic mastopathy. The later designation reflects its strong association with diabetes mellitus. The pattern of inflammation is however not specific to diabetes, presenting in a spectrum of autoimmune disorders, including autoimmune thyroiditis and Sjogren's syndrome.

Clinical features

The entity is most commonly associated with diabetes and the clinical features of diabetic mastopathy are:

- fibrotic breast lumps in patients with long-standing diabetes, commonly type 1 diabetes - much rarer in type 2.
- diabetes, usually insulin-dependent, has normally been present for 10 years or more and is often more severe than average and is often associated with other secondary complications.
- age range - mid 20s to mid 60s, but the tendency is towards younger women.
- may be seen in men and women.
- may be single or multiple lesions - bilateral in up to 50% of cases, may be synchronous.
- self-limiting but may recur - up to 30% in 15 years in one series.[1]
- ***not*** associated with an increased breast cancer risk or lymphoma.

Pathogenesis

The pathogenesis is unknown but a strong autoimmune association has been advocated. This is also supported by Lammie et al. who reviewed 13 cases of sclerosing lobulitis of the breast demonstrating an autoimmune association, including HLA DR and particularly DR3, 4 and 5 either alone or in combination.[2]

In diabetic mastopathy, both metabolic and autoimmune bases for the disease have been suggested. Possibilities include the development of mastopathy through an inflammatory or immunological reaction to exogenous insulin or a contaminant in the vehicle. But its occurrence in non-insulin-dependent diabetics indicates that this cannot be the only explanation. It is known that long-standing diabetes has pathological effects on connective tissue matrix, partly related to hyperglycaemia. These changes include reduced collagen turnover and degradation, which could be responsible for the accumulation of fibrous tissue. Also, as hyperglycemia induces extracellular accumulation of abnormal matrix and advanced glycosylated end products, an autoimmune reaction to these may act as neoantigens resulting in proliferation of B lymphoid cells and antibody formation.[3]

Pathology

Macroscopy: if the history is known it is possible to make this diagnosis on core biopsy, obviating the need for an operative procedure. If the lump is excised; it is poorly defined and fibrous without distinguishing features, although it is not usually infiltrative. Reported cases range from 0.8 to 6 cm in size.[4]

Microscopy: there is dense keloid fibrosis with a variable and often patchy perilobular, periductal and perivascular lymphoid infiltrate, associated with lobular sclerosis and atrophy (Figure 1). Atypical, occasionally bizarre or multinucleate cells

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are present in the stroma (Figure 2). Sometimes these are described as epithelioid or deciduoid, which could be mistaken for infiltrating carcinoma. These stromal cells are however cytokeratin negative and have been shown to express CD10, suggesting myofibroblastic differentiation.[5] It has been proposed that epithelioid stromal cells are specifically associated with diabetic mastopathy but other studies found that these are present in patients both with and without diabetes mellitus.[6]

Unlike other reactive infiltrates, the lymphoid population predominantly consists of small mature polytypic B lymphocytes rather than T lymphocytes. Intra-epithelial lymphocytes can be prominent and may form lymphoepithelial lesions, with increased expression of class II HLA DR by breast epithelium.[7] Although it is well established that certain autoimmune conditions at other sites are associated with B-cell non-Hodgkin's lymphoma, lymphocytic sclerosing lobulitis has not been recognised as a premalignant lesion.

The disease can show progression from dense inflammation to increasing lobular atrophy and fibrosis with decreasing inflammation. When these later changes occur, the appearances are less diagnostic as the most characteristic pathological feature is the circumscribed perilobular and perivascular lymphocytic aggregates.

Systemic lupus erythematosus

Clinical features

Lupus mastitis is a rare chronic inflammatory reaction of the subcutaneous fat and is a complication associated with SLE in 2–3% of cases.[8] This is usually between the ages of 20 and 50 years, with an occurrence two times greater in women than in men. The increased cancer risk is probably nil.[9] Rarely, lupus mastitis may be the initial presentation of this disease.

The presentation within the breast is typically in the form of a single or multiple subcutaneous nodules that may be tender or become painful. Epidermal changes such as atrophy or ulceration can also be present, mimicking inflammatory carcinoma. The lesions are ill-defined radiologically and can be associated with diffuse calcifications mimicking carcinoma.

Pathogenesis

SLE is a multisystem autoimmune disorder and the exact pathoaetiology of the disease remains unclear. Multiple genes contribute to disease susceptibility and a complicated multifactorial interaction with the hormonal milieu and environmental factors are involved.[10]

Pathology

Macroscopy: excision biopsy can usually be avoided if good cores are obtained and a good clinical history is supplied. Lesions are often firm 3 cm masses.

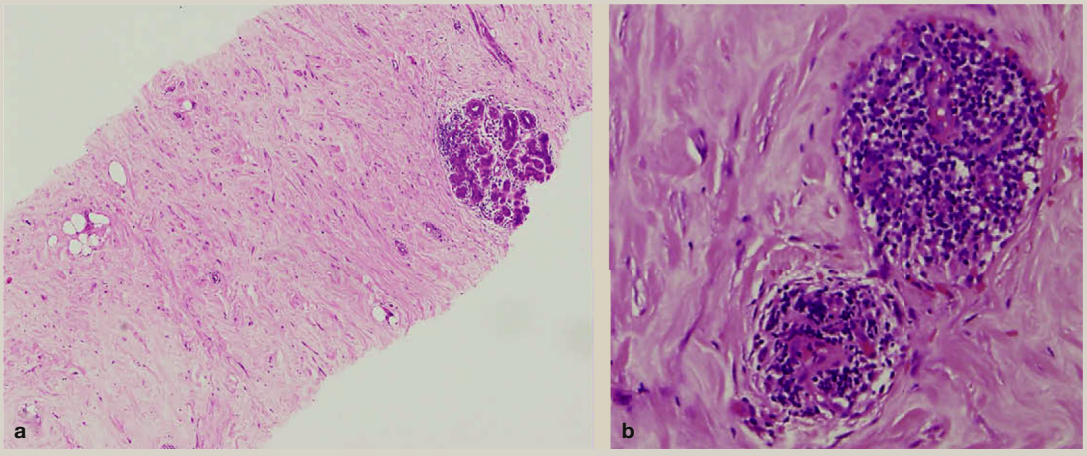
Microscopy: key features include:

- Perilobular, periductal and perivascular lymphoid infiltrate
- Periseptal (lobular) panniculitis
- Hyaline fat necrosis

Other findings comprise changes of discoid lupus erythematosus in the overlying skin: lymphocytic vasculitis, mucin deposition and hyalinization of the papillary dermis.

Vasculitides

It is exceptionally uncommon for vasculitis to present in the breast but Wegener's granulomatosis, giant cell arteritis and polyarteritis nodosa have all been described in the breast. The average age at presentation is in the mid-forties for Wegner's granulomatosis and in the mid-sixties for the latter two. Vasculitides can present as a breast mass which may be tender and bilateral. This can be complicated clinically by other features such as nipple retraction, generalized discolouration of the breast or peau d'orange. The histological features in the breast are the same as those described in other locations.[11] The major problem encountered by the pathologist is misdiagnosing a first clinical presentation in the breast as carcinoma.



Diabetic mastopathy. **a** Core biopsy showing stromal fibrosis and perilobular lymphocytic infiltration. **b** Detail of perilobular lymphocytic infiltrate.

Figure 1