Low grade marginal zone B cell lymphoma of the breast associated with localised amyloidosis and corpora amylacea in a woman with long standing primary Sjögren’s syndrome

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Primary low grade marginal zone B cell lymphoma (MZL) of the breast and localised mammary amyloidosis are exceedingly rare entities. This report describes the case of a woman with long standing Sjögren’s syndrome presenting with asymptomatic MZL of the breast showing plasmacytic differentiation, associated with local ductular amyloidosis. The lesion was discovered incidentally in breast tissue resected for microcalcifications. Immunohistochemistry revealed lambda light chain restriction, supporting the neoplastic nature of the infiltrate. A retrospective molecular study of the salivary gland biopsy showed a B cell clone. This is the first report of the association of human mammary ductular amyloidosis with cartwheel shaped material identical to corpora amylacea, usually seen in brain, lung, and prostate, but unknown in the human breast. The excellent outcome without treatment seen in this patient further emphasises the need to distinguish between MZL with plasmacytic differentiation and extramedullary plasmacytoma.

“Patients with Sjögren’s syndrome have a 44 fold increased risk of developing lymphoma”

CASE REPORT

A 37 year old woman with a 10 year history of primary Sjögren’s syndrome presented with left axillary lymphadenopathy and radiographic microcalcifications of the left breast. Sjögren’s syndrome, first manifested by arthralgias and xerostomia, was confirmed by lymphocytic Chisholm grade IV infiltration of the accessory salivary gland. The patient had remained asymptomatic during 10 years of follow up. However, routine monitoring demonstrated persistent lymphopenia (3600 white blood cells/mm³) and a slightly raised erythrocyte sedimentation rate (40 mm/1st hour), probably as a result of polyclonal hypergammaglobulinemia (25 g/litre).

Tests for antinuclear antibodies (SSA) and rheumatoid factors (latex, 1/60; Waaler Rose, 1/80) were positive; cryoglobulins were detected. In November 1998, a mobile lymphadenopathy was found in the left axillary area, with no palpable breast mass or other physical abnormality. Mammography visualised a focus of microcalcifications within the left breast. Computerised thoracic and abdominal tomographic examination did not show internal lymph nodes or splenomegaly. The left axillary node and breast microcalcifications were surgically excised and subjected in their entirety to histological examination.

Pathological findings

The axillary node showed no major histological changes. The breast stroma contained a dense cellular infiltrate aggregated exclusively around ductules, the lumens of which were entirely filled with eosinophilic material (fig 1A). The cellular infiltrate comprised lymphoid cells with slightly irregular nuclei admixed with mature plasmacytes. No lymphoid follicles were seen. The lobular structure was maintained, except in some areas where focal lymphoepithelial disruptions were seen.

The eosinophilic material comprised foci of microcalcifications, which were surprisingly associated with periodic acid Schiff (PAS) positive, sharply delineated round structures resembling corpora amylacea (fig 1B). Congo red staining was positive and polarised light induced green birefringence (fig 1C) that persisted after 5% potassium permanganate pretreatment, thereby indicating that it was not AA amyloid type. In addition, crystal violet staining was positive and thioflavine T staining demonstrated characteristic apple green fluorescence.

Ultrastructural study

A formalin fixed, paraffin wax embedded breast specimen was cut into small blocks of about 1 mm³, washed in phosphate buffered saline (PBS) and sequentially fixed in PBS buffered 2% glutaraldehyde for four hours and 1% osmium tetroxide for one hour, then dehydrated in graded alcohol, embedded in epoxy resin, and submitted for ultrastructural analysis according to standard procedures for electron microscopy. The framework of amorphous Congo red positive deposits consisted of aggregates of non-branching filaments haphazardly distributed (fig 2A). Areas of sharply delineated structures resembling corpora amylacea demonstrated spherical masses of fibrillary material displaying radial organisation (fig 2B).

Abbreviations: MZL, marginal zone B cell lymphoma; PAS, periodic acid Schiff; PBS, phosphate buffered saline
Immunohistochemical labelling

Anti-CD20 (clone L26) labelled most of the cells surrounding mammary ductules. Antibodies to CD5 (clone 4C7), CD23 (clone 1B12), and CD10 (clone 56C6) were negative. Lymphoepithelial lesions (fig 1D) were recognised by anticytokeratin antibody (clone KL1). Strong κ light chain restriction was demonstrated (fig 1E) with only rare λ positive normal cells (fig 1F). The negativity of anti-amyloid AA serum (clone mc1) confirmed the previous results. Because the breast biopsy had been fixed, molecular characterisation of the light chains was not possible. The axillary node did not demonstrate light chain restriction.

Molecular study

Clonal rearrangements of the immunoglobulin heavy and light chain genes were detected retrospectively in the frozen
Follow up

After 3.5 years of follow up without treatment, the patient has remained free of local MZL recurrence and visceral dissemination. Histological evaluation of medullary bone and rectal mucosa biopsies failed to demonstrate systemic amyloidosis.

DISCUSSION

We describe a patient with Sjögren’s syndrome in whom asymptomatic breast microcalcifications revealed a primary mammary MZL associated with localised deposits of amyloidosis admixed with corpora amylacea. Although the overall feature of this lesion was similar to that of a plasmacytic lobulitis, foci of lymphoepithelial destruction and κ light chain restriction supported the diagnosis of MZL. The search for clonality in the breast specimen could not be performed because of previous fixation.

“Ductal amyloidosis represents another unusual finding in our patient because it has rarely been associated with marginal zone B cell lymphoma”

The increased incidence of low grade B cell clones emerging in patients with autoimmune disorders is established. MZLs develop in lymph nodes or extranodal sites, and are usually found in the gastrointestinal mucosa, lung, thyroid, parotid, and conjunctiva. MZL of the breast is exceedingly rare. Thieblemont et al studied 108 patients with MZL and in only two cases were the tumours breast related. Two cases have been reported in association with autoimmune disease: one case associated with local stromal amyloidosis in a woman with systemic lupus erythematosus and another without amyloidosis in a woman with Sjögren’s syndrome. Schwartz and Strauschen described eight women with lobulocentric B cell type hyperplasia of the breast, referred to as “lymphoepithelial mastopathy”, three of whom presented with autoimmune disorders, but there was no evidence of a plasmacyte component associated with light chain restriction.

Ductal amyloidosis represents another unusual finding in our patient because it has rarely been associated with MZL: only once each in breast stroma and vessels, jejuno-ileal mucosa, and salivary glands, in addition to six cases of pulmonary MZL. Although we could not demonstrate light chains immunohistochemically, the ductal amyloidosis is probably secreted with immunoglobulin light chains. Surprisingly, the amorphous deposits in our case, which comprised typical ultrastructural amyloid fibres (fig 2A), were associated with spheroid PAS positive and Congo red positive structures resembling corpora amylacea, often seen in brain, lung, and prostate but unknown in human breast. In our case, ultrastructural examination of these structures showed aggregates of radiating fibrils in a parallel arrangement. Congo red positive corpora amylacea with similar ultrastructural features were observed by veterinary pathologists in canine and bovine mammary tissue. There is no consensus concerning the mechanisms involved in the formation of corpora amylacea. The prevailing theory in bovine mammary tissue is that they originate from a matrix of organic material derived from casein with crystalline hydroxyapatite and local deposits of β2 microglobulin. Finally, the exceptional role of microcalcifications in the revelation of this asymptomatic breast MZL should be kept in mind. It emphasises the need for careful clinical examination of nodes and extranodal organs supposedly affected by MZL in patients with long standing autoimmune disorders.

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New chemokines may have a role in vernal keratoconjunctivitis

New attractants of T lymphocytes and several activation factors contribute to inflammation in vernal keratoconjunctivitis (VKC), a molecular study has found. The findings may help to explain how T lymphocytes are recruited to the conjunctiva.

Three chemokines—pulmonary and activation regulated chemokine (PARC), macrophage derived chemokine (MDC), and 1-309, the MDC receptor CCR4—strongly attractive to T lymphocytes were present in the cytoplasm of inflammatory cells in sections of conjunctivas from patients with VKC. PARC predominated, appearing in all specimens and in many more of the abundant CD3+ T lymphocytes in the upper substantia propria. MDC and 1-309 showed up in nine and six specimens, respectively.

Among five activation factors tested, CD25 occurred in significantly more T lymphocytes than the others. The mean cell numbers for the remaining factors were significantly different from each other and were, in descending order, CD26, CD62L, CD71, and CD30. CD25 also showed a strong link with CD3+ T lymphocytes and with the number of cells expressing PARC. Conjunctivas from controls with no inflammation were weakly positive only for CD26.

Biopsy specimens of limbal conjunctiva were taken from 11 Saudi children with active disease and eight control children of similar age having an operation for strabismus. Thin sections were stained immunohistochemically for each chemokine and activation factor.

How and why T lymphocytes present in this chronic inflammatory condition migrate to the conjunctiva is not understood. So the new chemokines were prime candidates for study.

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