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Localized AL Amyloidosis in a Patient with Diffuse Large B-cell Lymphoma of the Breast

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Amyloidosis refers to a variety of conditions in which a protein polysaccharide complex, amyloid protein, is accumulated locally or systemically in tissues or organs. Amyloid in the skin may be derived directly from keratinocytes, or secondarily from immunoglobulin light chain fragments (AL type), fragments of the acute-phase reactant serum amyloid A (AA type), etc. Nodular amyloidosis (NA) is a rare type of localized AL amyloidosis, with most reported cases being of the lambda light chains (1) and is often histopathologically indistinguishable from systemic amyloidosis. Its association with lymphoma has been observed infrequently.

CASE REPORT

An 88-year-old woman initially noticed a 5×3 cm mass in her right breast in 1990. She was diagnosed with non-Hodgkin's lymphoma (NHL) (diffuse large immunoblastic B-cell type, stage IE) after the excision of the mass in a tertiary referral centre. Bone marrow biopsy revealed no evidence of lymphoma involvement. She achieved complete remission after chemotherapy. Six years after the diagnosis of lymphoma she developed multiple enlarging nodules on her legs. On examination, there were coalescing, waxy, skin-coloured, nodules with some foci of haemorrhage, central ulceration and crusts on the legs (Fig. 1). Skin biopsy revealed homogenous, eosinophilic, amorphous nodular deposit of amyloid in the dermis, with involvement of the blood vessel walls (Fig. 2A). Lymphoplasmacytic cells aggregation with erythrocytes extravasation was also observed. Congo red stain revealed green birefringence under polarized light (Fig. 2B). Transmission electron microscopy showed some rigid, straight, 6–10 nm-sized, non-branching filaments. No restrictive cardiomyopathy or hepatosplenomegaly was found by whole-body computer tomography and echocardiogram. Random biopsy of rectal mucosa and abdominal skin did not demonstrate amyloid deposits. Technetium-99m-pyrophosphate (Tc-99m PYP) scintigraphy showed multifocal areas of increased uptake of Tc-99m PYP in the subcutaneous tissues of the legs and right thigh. Laboratory investigations showed a positive antinuclear antibody with a titre of ≥1:1280 in a speckle pattern and an anti-centromere antibody with a titre of ≥1:1280. Urine immunofixation electrophoresis (IFE), bone marrow biopsy, anti-double-stranded DNA, anti-Ro (SSA) and anti-La (SSB) autoantibodies were all negative. IFE was initially negative, but detected an IgG λ monoclonal gammopathy 7 years after the skin biopsy. Based on the patient's clinical, pathological, and laboratory data, she was diagnosed with NA associated with diffuse large B-cell lymphoma of the breast. She subsequently received intralesional triamcinolone acetonide (5 mg/ml), Super Lizer™ infrared light and topical psoralen plus ultraviolet-A (PUVA) therapy, but NA progressed. Only partial response to topical PUVA was observed. The nodular lesions became ulcerated and haemorrhagic and were complicated with several episodes of cellulitis in the following years. Besides, her lymphoma relapsed in 2004.

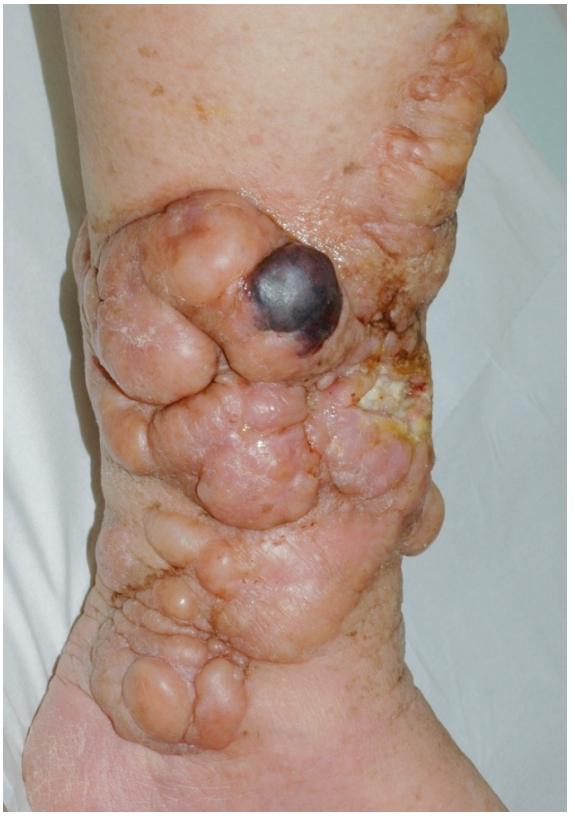

Fig. 1. Multiple waxy, skin-coloured, verrucous nodules with some foci of haemorrhage and central ulceration involving the entire lower legs.

DISCUSSION

NA is a localized cutaneous AL amyloid deposit with a tendency to affect acral sites. It may be primary or associated with autoimmune and lymphoproliferative disorders. The exact mechanism of NA remains unclear. Gene rearrangement studies have confirmed clonality of the amyloid-producing plasma cells in the skin, but not in the bone marrow, and suggested that NA might arise from local plasma cell dyscrasia or plasmacytoma (1). Several disorders, including systemic sclerosis, primary biliary cirrhosis, systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis, have been associated with NA (2).

NHL of the breast, a rare malignancy, accounts for approximately 2.2% of extranodal NHL and 0.2% of breast malignancy (3). Diffuse large B-cell lymphoma was the predominant histological type (3). Monoclonal gammopathy had been found in 2.4% of adult patients with NHL (4). Amyloid deposition associated with

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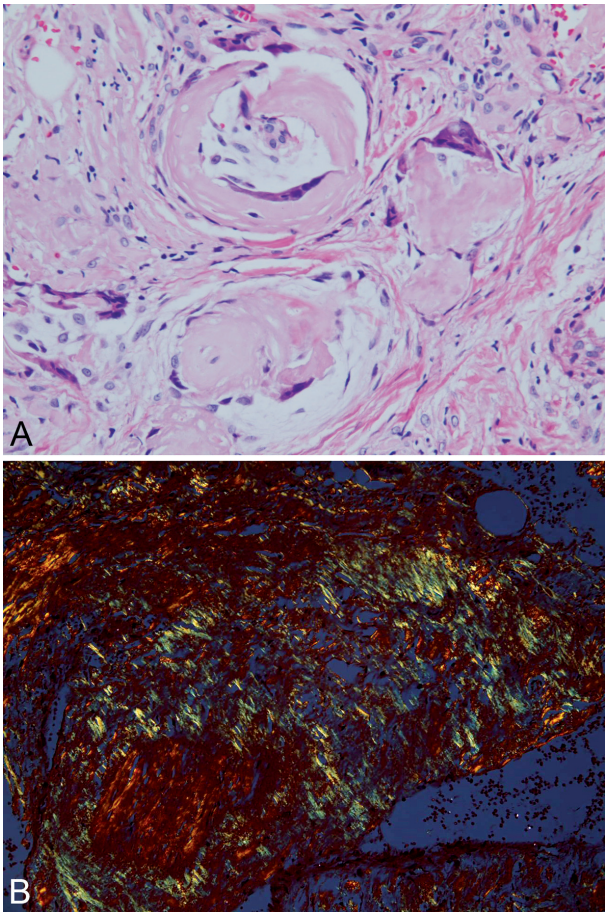

Fig. 2. (A) Homogenous, eosinophilic, amorphous nodular deposition of amyloid in the dermis with involvement of the blood vessel walls (haematoxylin and eosin stain; original magnification ×400). (B) Green birefringence on Congo red stains viewed under polarized light.

NHL, which can be systemic (5) or localized (6), had been reported. In most patients, amyloidosis is usually AL-type, and AA-type amyloidosis (7) in patients with NHL is extremely rare. Local amyloid deposits are usually localized in areas adjacent to the lymphoma (7) and had been found in nasal sinuses, lung, urinary tract, tongue, gastrointestinal tract, breast, brain, and soft tissues, despite the presence of circulating light chains (5). NA associated with NHL is rare and only one case of a lymphoplasmacytoid lymphoma with NA of salivary gland extending to the skin had been reported (6). However, lymphoma with non-co-localized cutaneous amyloid deposition had not been reported.

In 1970, Brownstein & Helwig (8) reported a 50% progression rate of primary cutaneous NA into systemic amyloidosis in a case series of 10 patients. However, recent studies by Woollons & Black. (9) and Moon et al. (10) showed that systemic amyloidosis progression rate was 7% in two independent studies, of 15 patients, respectively.

Clinical features of NA are variable and need to be differentiated with colloid milium, sarcoidosis, pseudolymphoma, deep fungal infection, nodular pretibial myxoedema, elephantiasis nostras verrucosa, neoplasms and other deposit diseases. Treatment of NA is often difficult, and our case also showed that various treatments, such as intralesional steroid, PUVA and Super Lizer™, were disappointing.

Although immunohistochemical staining was negative for lambda and kappa light chains on amyloid deposits in our patient, clinical appearance of waxy nodules combined with amyloid deposits on skin biopsy favoured the diagnosis of nodular amyloidosis (localized AL amyloidosis). Because no other possible aetiology possibly leading to amyloidogenesis, such as pruritic dermatoses, could be identified, and due to the development of NA in our lymphoma patient with monoclonal gammopathy, we reasonably thought that there was an association between NA and lymphoma. However, our case report provided limited proof for this connection.

In summary, complete evaluation at initial diagnosis with subsequent follow-up for systemic amyloidosis, autoimmune disease and lymphoproliferative disorders is indicated in patients with NA.

The authors declare no conflict of interest.

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