Bullous Amyloidosis Mimicking Bullous Pemphigoid: Usefulness of Electron Microscopic Examination

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Bullous amyloidosis is a rare cutaneous manifestation of systemic AL amyloidosis that may be associated with multiple myeloma or occult plasma cell dyscrasia (1–3); only approximately 30 cases have been reported until now (4, 5), although its incidence may be higher than is generally believed (3). Interestingly, the patient described here was found to have plasma cell dyscrasia only after the occurrence of bullous amyloidosis. The histopathological picture mimicked that of bullous pemphigoid because of equivocal positivity for specific amyloid staining, but electron microscopy (EM) of the deparaffinized, formalin-fixed tissue demonstrated aggregation of amyloid fibrils, which was useful for diagnosing cutaneous amyloidosis in this case.

CASE REPORT

An 85-year-old Japanese man with senile dementia was referred to our hospital. His family had noticed pruritic erythematous eruptions on his trunk and extremities 2 months previously. Topical corticosteroid was ineffective, and bullous lesions had emerged prior to the consultation. On physical examination, he showed multiple vesicles and tense bullae of an irregular shape, some of which were haemorrhagic. They either accompanied erythema or occurred on apparently normal skin. Erosions, excoriations, crusts and hyperpigmentation were noted (Fig. 1). The truncal eruptions were observed mainly around the waist, suggesting that they might be triggered by mechanical stimuli. He showed no mucosal involvement and no other symptoms suggestive of systemic amyloidosis, and bullous pemphigoid was suspected as an initial differential diagnosis. Histopathology showed a subepidermal blister with normal epidermis (Fig. 2a). Inflammatory cell infiltration was observed in the dermis, with many eosinophils both in the dermis and blister fluid (Fig. 2b). Serum anti-BP180 antibody, and anti-desmoglein 1 and 3 antibodies, were negative, and direct immunofluorescence revealed no immunoglobulin or complement deposits in the basal membrane zone or dermis. Laboratory examination showed anaemia (haemoglobin: 9.5 g/dl) and eosinophilia (910/mm^3; 11.8% of white blood cells), with a slight decrease in platelet counts (99,000/μl). Serum total protein was 10.6 g/dl with low albumin (3.0 g/dl), and protein electrophoresis demonstrated a monoclonal immunoglobulin G (IgG) kappa band with high serum IgG (6280 mg/dl; normal: 870–1700 mg/dl), and low serum IgM (20 mg/dl; normal: 35–220 mg/dl) and IgA (54 mg/dl; normal: 110–410 mg/dl). The serum IgE level was 7 IU/ml, and serum eotaxin and interleukin-5 levels were not elevated (61.1 and < 7.8 pg/ml, respectively). He also showed renal dysfunction, with a serum creatinine level of 2.06 mg/dl (normal 0.4–0.7 mg/dl) and urine protein concentration of 50 mg/dl, but the measurement of urine protein could not be performed. Overall, these findings indicated the diagnosis of plasma cell dyscrasia, and bullous amyloidosis as a manifestation of systemic AL amyloidosis was suspected for the skin lesions. Immunohistochemical staining, however, failed to detect immunoglobulin kappa and lambda chains. Amyloid deposits were equivocal on employing specific amyloid staining with Congo red derivative 1-fluoro-2,5-bis(3-carboxy-4-hydroxystyryl)benzene (FSB), and showed only as a very weak apple-green birefringence under polarized light. EM investigation of the deparaffinized, formalin-fixed tissue samples finally confirmed the presence of non-branching amyloid fibrils (Fig. 2c). Before undergoing further examination, including bone marrow biopsy, the patient was admitted to another hospital because of loss of consciousness caused by hypercalcaemia, and died 4 months later without active treatment.

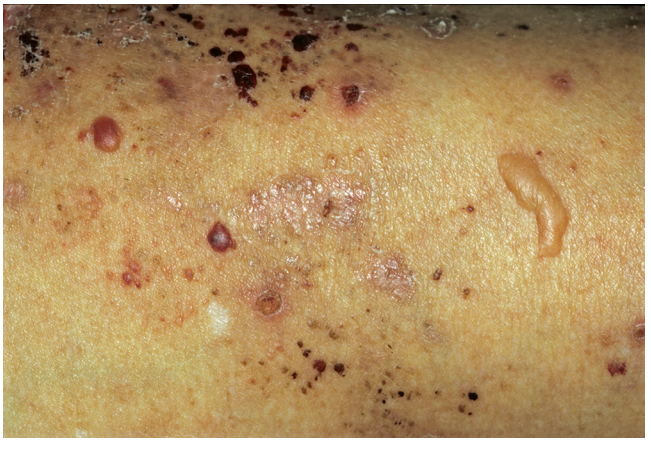

Fig. 1. Clinical picture of the left thigh showing multiple haemorrhagic vesicles and tense bullae, together with erythema, crusts and hyperpigmentation.

DISCUSSION

Cutaneous and mucous involvement is relatively common in patients with systemic AL amyloidosis (1–3). Its typical manifestations include pinch purpura, waxy papules, nodules, plaques, and macroglossia, while bullous lesions are infrequent (1, 2). Bullae in bullous amyloidosis are consecutive to either subepidermal or intradermal clefting (1–3), and differential diagnoses include bullous pemphigoid, epidermolysis bullosa acquisita, linear IgA disease, bullous drug eruption, bullous lupus erythematosus, porphyria cutanea tarda, and pseudoporphyria (1, 2, 4). In the present case, mucous and periorbital lesions, typical of systemic AL amyloidosis (6) were absent. The presence of erythema and blood/tissue eosinophilia with subepidermal blisters favour the diagnosis of bullous pemphigoid in elderly patients. In fact, it is uncommon to find dermal inflammation in bullous amyloidosis, except for a few reported cases (1, 2, 4), and pruritus has been reported

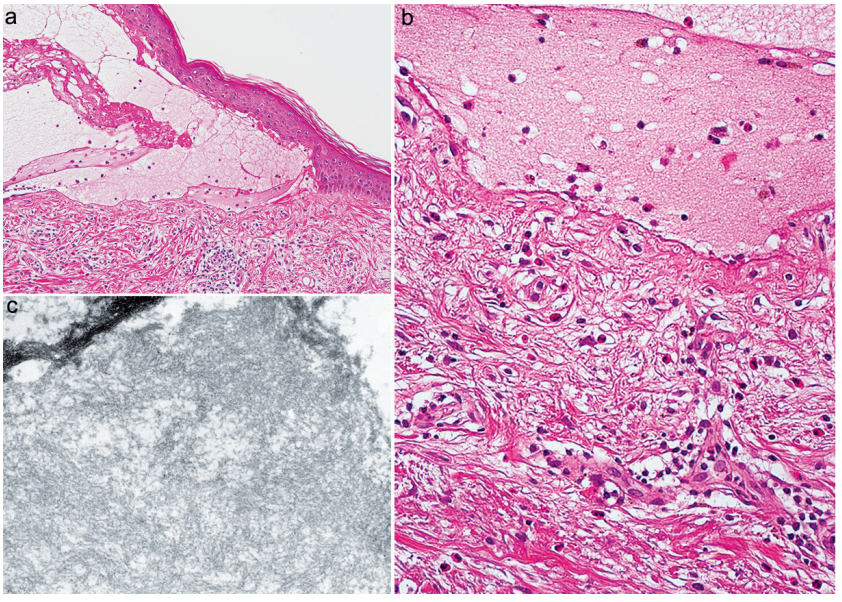

Fig. 2. (a) Histopathological picture of a subepidermal blister with normal epidermis (haematoxylin and eosin (H&E); original magnification: ×200). (b) A closer view of the blister showing inflammatory cell infiltration containing eosinophils, both in the dermis and blister fluid (H&E; original magnification: ×400). (c) Electron microscopy of the deparaffinized, formalin-fixed tissue demonstrating the aggregation of non-branching amyloid fibrils beneath the blister (original magnification: × 25,000).

only rarely (2, 4). Similar to the present case, a case reported by Johnson et al. (2) was initially diagnosed as bullous pemphigoid because of a subepidermal blister with infiltration of eosinophils. The possibility of bullous pemphigoid or other autoimmune bullous dermatoses was nevertheless unlikely in our case, based on the negative direct immunofluorescence study and absence of serum anti-BP180. In bullous amyloidosis, amyloid deposits of AL-type (3) or more rarely of AA-type (5) have been demonstrated. Importantly, AL amyloid deposits were difficult to detect by specific amyloid staining, and indeed, in three reported cases (1, 2, 7), EM was helpful to confirm the diagnosis of bullous amyloidosis. EM of deparaffinized, formalin-fixed tissue blocks clearly demonstrated the presence of amyloid deposits in the present case, and we avoided repeated biopsies (2, 7) for this purpose.

Some hypotheses have been proposed regarding the mechanism of blistering in bullous amyloidosis, such as the fragility of amyloid-laden dermal connective tissue and engulfment or transepidermal elimination of dermal amyloid deposits (2, 8). In our case, it is tenable that inflammatory cell infiltration also played a role in blistering. However, blood eosinophilia has been shown to accompany multiple myeloma in rare instances (9), regardless of cutaneous manifestations. Moreover, in the present case the patient's serum eotaxin and interleukin-5 levels were not elevated, both of which are often detected at high levels in bullous pemphigoid and are considered to contribute to eosinophil accumulation in the skin (10). More studies of similar cases are necessary to come to any conclusion.

In many cases (1–5, 7, 11), bullous amyloidosis leads to the discovery of underlying plasma cell dyscrasia or multiple myeloma. Although the prognosis for systemic amyloidosis is unfavourable, the early recognition, diagnosis, and treatment of complications can help to decrease the morbidity and mortality of this disease (2). Haemorrhagic bullae serve as a clue to the diagnosis of bullous amyloidosis (1, 2, 11).

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