Primary nodular cutaneous amyloidosis—long-term follow-up and treatment

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Summary
A case of facial primary nodular cutaneous amyloidosis is reported. This illustrates: the striking appearance of this unusual condition; the investigations appropriate to establish the diagnosis and to exclude underlying systemic amyloidosis or a condition which might contribute to amyloidosis; and the difficulty of successful management. Initial investigation failed to reveal any evidence of systemic amyloidosis or an associated internal illness. Two amyloid nodules were excised, but 7 years later the patient developed further nodules on the adjacent facial skin and again sought dermatological advice. He was reinvestigated and again no underlying condition was found. A trial of cryotherapy was unsuccessful, but curettage and cautery produced a cosmetically acceptable result.

The amyloidoses are a group of rare conditions characterized by extracellular deposition of several different unrelated proteins which share histological, immunofluorescence and ultrastructural features. They are categorized according to their clinical features and the nature of the amyloid deposits. Three types of primary cutaneous amyloidosis are recognized. Lichen amyloidosis and macular amyloidosis are the most common, and are associated with deposition of a type of amyloid protein in the upper dermis which appears to be derived from epidermal cells.1 2 The third type, nodular or tumefactive primary cutaneous amyloidosis, is very rare, however, and only some 50 cases have been reported since it was first described in 1950.3 4

Primary nodular cutaneous amyloidosis is thought to be formed by deposition of amyloid L protein in the dermis and subcutis produced by a local plasma cell dyscrasia. The amyloid chains in this condition are indistinguishable from those which may be deposited in the skin and other tissues as a complication of primary systemic amyloidosis, which is usually associated with evidence of a systemic plasma cell dyscrasia or of multiple myeloma. Investigation of patients with nodular cutaneous amyloidosis may reveal evidence of systemic amyloidosis, paraproteinaemia, a plasma cell dyscrasia or myeloma;1 5 occasional patients presenting with primary nodular cutaneous amyloidosis develop multiple myeloma several years later.1 6 7 However, at least 38 cases of primary nodular cutaneous amyloidosis have been reported without evidence of systemic involvement. Very rarely, clinically apparent cutaneous amyloid deposits may occur in secondary systemic amyloidosis which may complicate infective or inflammatory conditions, or familial diseases such as Mediterranean fever or Muckle-Wells' syndrome.1 8 Usually, however, such cutaneous deposits are asymptomatic or only present because of mild haemorrhage from adjacent cutaneous blood vessels.8 9

Therefore patients with nodular cutaneous amyloidosis should be investigated and followed up, to exclude associated systemic amyloidosis or an underlying disease which might contribute to it. We report a case of primary nodular cutaneous amyloidosis which illustrates the striking clinical appearance of this condition, and the difficulty of managing it successfully in the absence of any treatable underlying cause.

Case report
A 35-year-old man was referred to the dermatology clinic with a 1-year history of two slowly growing pearly nodules affecting the upper right nasolabial fold and the left side of his chin (Fig. 1a and b). The lesions had a glistening, gelatinous appearance with a translucent attenuated epidermis stretched over the surface and foci of telangiectasia within. The clinical differential diagnosis included nodular amyloidosis, acquired haemangioma, basal cell carcinoma, adnexal tumours, infiltration by a lymphoma or sarcoidosis. He was otherwise well and his previous medical history had been uneventful, apart from...
from mild rosacea 7 years previously which had responded to systemic oxytetracycline and topical 0.5% sulphur in calamine lotion, both of which he had discontinued 3 years later.

Superficial incisional biopsies and subsequent excisional biopsies of both lesions revealed similar histological features (Fig. 2). There was a nodular expansion of the papillary and reticular dermis by homogeneous, eosinophilic material. The features, subsequently confirmed by Congo-red affinity with apple-green birefringence, were typical of amyloid. The material lay in the upper dermis, as an irregular band at the dermo-epidermal junction, and in the walls of small blood vessels. The deeper dermal component was more expansile and nodular with apparent compression of skin appendages. In the mid and deeper reticular dermis there were aggregates of plasma cells lying in association with the amyloid. These were morphologically normal with a typical chromatin pattern and cytoplasmic amphophilia with no blast transformation. Within the nodular aggregates, there was a focal granulomatous giant cell reaction to the amyloid deposition.

The amyloid stained weakly with a monoclonal antibody to kappa light chains and the plasma cells were polytypic with a ratio of approximately 2:1 IgG kappa to lambda staining cells. There was no obvious heavy chain production, i.e. the pattern was 'non-secretory'. Electron microscopy revealed typical irregular, haphazard non-banded amyloid fibrils, approximately 7-10 nm in diameter. Potassium permanganate failed to remove the congophilia, confirming that the amyloid was not of secondary 'inflammatory' type.
The following investigations, performed to exclude the presence of an underlying condition which might contribute to systemic amyloidosis, were normal: full blood count, erythrocyte sedimentation rate, plasma urea, glucose and electrolytes, liver function tests, prothrombin index, thyroid function, serum electrophoresis, immunoglobulin and complement levels, auto-antibody profile, rheumatoid factor, syphilis serology, hepatitis B surface antigen; urine dipstick analysis, microscopy, culture, electrophoresis and testing for Bence Jones proteins after concentration; intradermal tuberculin test (10 units); chest X-ray, abdominal ultrasound, electrocardiogram and a biopsy of normal-looking abdominal skin.

The patient was satisfied with the cosmetic results of the surgery and declined further investigation. However, further nodules of amyloid accumulated in skin adjacent to the excision sites over the subsequent 7 years (Fig. 3). He was therefore reinvestigated as before but again no evidence of systemic amyloidosis emerged nor of any illness which might predispose to its development; he declined a rectal biopsy, bone marrow trephine or aspiration and a skeletal survey.

On this occasion it was felt that further radical surgery was not appropriate since it was impossible to be certain that the lesions might not recur. A preliminary trial of cryotherapy was unhelpful and complicated by minor haemorrhage, and so the lesions were removed gradually, in three episodes of curettage followed by cautery under local anaesthetic, at 2-monthly intervals, which produced a satisfactory result (Fig. 4).

Discussion

The clinical and histological features were typical of primary nodular cutaneous amyloidosis in which the amyloid deposits contain amyloid L derived from immunoglobulin light chains.1 The precise source and nature of the amyloid fibril protein in the muscular and papular (lichen amyloidosus) forms of primary cutaneous amyloidosis is, however, controversial but it appears to be derived from epidermal cells.1,2 In the nodular form the presence of plasma cells suggests a localized form of plasma cell dyscrasia, although full investigation is required to exclude primary systemic amyloidosis due to a systemic plasma cell dyscrasia or multiple myeloma. In this case there was no evidence of either systemic amyloidosis or of a condition which would predispose to it, but, although the subject was investigated on two occasions, he declined several important investigations listed above.

B-cell clonality of bone marrow cells has recently been demonstrated by gene rearrangement in patients with nodular cutaneous amyloid deposits due to primary systemic amyloidosis, either with or without associated overt myeloma or paraproteinaemia. Clonality of the amyloid-producing plasma cells from cutaneous nodules in two further patients with primary localized nodular
cutaneous amyloidosis has also been demonstrated but without accompanying clonality of their bone marrow cells.\textsuperscript{5,10} This confirms that the cutaneous amyloid deposits in primary nodular cutaneous amyloidosis may arise in relation to a localized plasmacytoma.\textsuperscript{5,10} T-cell marker studies of the cutaneous amyloid deposits in two such patients have also shown that many of the infiltrating lymphocytes were T-cells (CD3, CD5, CD4 > CD8), perhaps having a regulatory role in production of the amyloid.\textsuperscript{10} Unfortunately, similar studies were not possible in our patient.

Dermabrasion,\textsuperscript{11} etretinate\textsuperscript{12,13} and topical dimethyl sulphoxide\textsuperscript{14} have been tried for the treatment of lichen amyloidosus with conflicting results. Most cases of nodular cutaneous amyloidosis are treated with excision which also provides material for histological and electron microscopical confirmation of this rare condition. However, it has the tendency to recur,\textsuperscript{1} as happened in our patient, presumably because the surgical procedure did not remove all of the abnormal plasma cells. For this reason, a less radical surgical approach was chosen on the second occasion. Carbon dioxide laser therapy has been used successfully for treating this condition but may be associated with recurrence,\textsuperscript{15} and variable results have been reported with cryotherapy\textsuperscript{16,17} which was unhelpful here. Shave excision\textsuperscript{18} and electrodesiccation with curette\textsuperscript{16} have also been reported to be suitable treatments for nasal deposits of nodular cutaneous amyloidosis, and a very acceptable cosmetic result was produced in this case.

References

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