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Case report

Systemic amyloidosis — three illustrative cases

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Amyloidosis is characterised by the extracellular deposition of abnormal protein fibrils. Recent advances in the study of amyloidosis have been based on the chemical analysis of these protein fibrils.[1,2] This has also led to a more rational classification of the condition (Fig 1). Further discussion of localised forms of amyloidosis is outside the scope of this article, which will be confined to systemic amyloidosis.

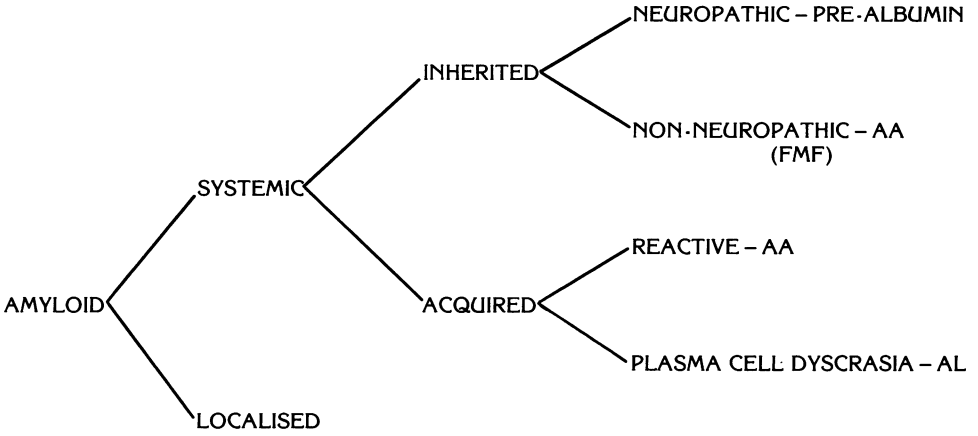

Fig 1. *Classification of amyloidosis*

Systemic amyloidosis may be either inherited or acquired. The neuropathic forms, which show an autosomal dominant inheritance, predominantly affect peripheral nerves, but may involve also the heart, kidneys and other tissues. The protein fibrils are derived from circulating prealbumin, which has an inherited abnormality in the amino acid sequence in some kindreds.[3] The most studied form of inherited non-neuropathic amyloidosis is familial Mediterranean fever (FMF). This autosomal recessive disorder is confined to populations originating on the southern and eastern coasts of the Mediterranean Sea. It is characterised

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by recurrent acute inflammatory attacks of various types (abdominal pain, polyserositis, arthritis, skin rashes) and the gradual deposition of amyloid protein, most notably in the kidneys. The amyloid fibrils in FMF are derived from a circulating acute phase reactant known as serum amyloid A (SAA) protein. Serum amyloid A is also the major precursor protein of acquired reactive systemic amyloidosis (AA amyloid). This may occur as a complication of chronic inflammatory diseases such as rheumatoid arthritis or chronic infection, and was previously classified as secondary amyloidosis.

The other main type of systemic amyloidosis is AL amyloid, which is derived largely from the variable regions of immunoglobulin light chains, secreted by a clone of plasma cells. This clone may give rise to overt myeloma with features such as lytic lesions in bone but may also present solely as amyloidosis. Such cases were previously classified as primary amyloidosis.

Amyloidosis is an uncommon condition, with a wide variety of clinical presentations, and for this reason the diagnosis may be overlooked. Three cases presented to a general medical ward within a three-month period. We describe these cases to illustrate the diverse features of the disorder.

CASE 1

A 62-year-old lady presented with swollen salivary glands and mild cardiac failure. She also complained of dysphagia, loss of hair, episodes of spontaneous bruising around the eyes, and aching muscles. She had been well until one year previously when she had complained of aching leg and back muscles on exertion and had had an operation for spinal stenosis, without improvement in her symptoms. On examination, the submandibular glands were enlarged and had a firm rubbery consistency, the tongue was grossly enlarged and showed indentations made by her teeth (Fig 2). The skeletal muscles were enlarged and indurated to give an incongrous brawny appearance (American footballer or shoulder pad sign). Biopsy of deltoid muscle showed extensive infiltration of the interstitium with amyloid which was permanganate resistant. Biopsy of the rectum contained mucosa only and did not contain any amyloid. A type G-lambda paraprotein was present in the serum (6g/l) and urine (0.7g/l). Bone marrow trephine revealed a moderate increase in plasma cells (15%). No lytic lesions were present on skeletal survey and other investigations revealed normal haemoglobin, urea and serum albumin concentrations and ESR of 25 mm/hr. An electrocardiogram (ECG) showed low voltage complexes.

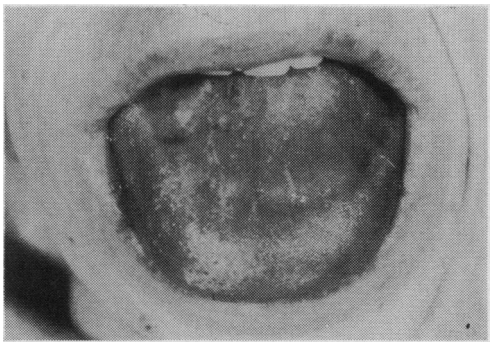

Fig 2. Case 1. Enlarged indurated tongue with indentations made by the lower teeth.

The cardiac failure was easily controlled by diuretics. A course of melphalan and prednisolone was given but there was no reduction in the serum paraprotein concentration. The most disabling symptoms were dysphagia due to progressive enlargement of the tongue and generalised muscular weakness. The patient died nine months after diagnosis from a respiratory arrest.

CASE 2

A 62-year-old man presented with oedema due to nephrotic syndrome and cardiac failure. He had been previously well. Urinary protein loss was 6g/24 hours (normal less than 0.15g) and serum albumin was reduced to 16g/litre (normal 35 – 50). However, renal function was preserved as indicated by a normal urea concentration 5.1 mmol/l (3 – 6). A type G-lambda paraprotein was present in the serum (10g/l) and urine (concentration not measured). The kidneys showed increased echogenicity on ultrasound examination. ECG showed low voltage complexes. The cardiac failure and oedema proved resistant to intensive treatment with diuretics and albumin infusions. Melphalan and prednisolone therapy was commenced, but the patient died from a bleeding duodenal ulcer five weeks after presentation. At autopsy, the heart, kidneys, spleen and liver were heavily infiltrated with amyloid which was permanganate resistant. The blood vessels in the base of the duodenal ulcer were also infiltrated with amyloid. There were large numbers of plasma cells in the bone marrow (proportion not estimated).

CASE 3

A 58-year-old man was referred for investigation of diarrhoea. Two years previously he had developed cardiac failure and was diagnosed as having amyloid heart disease by endomyocardial biopsy at the Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast. Prior to this, he had been healthy, with no history of chronic inflammatory disease, ischaemic heart disease or hypertension. He was of Anglo-Irish descent with no family history of amyloidosis. On his initial presentation he underwent extensive cardiac investigation. ECG showed sinus rhythm, some reduction in voltage of the limb lead complexes and T wave inversion in leads, 11, 111, AVF, V1 – V4. Echocardiographic appearances were consistent with a cardiac infiltration. A pyrophosphate radioisotope scan demonstrated diffuse intense uptake of the isotope by both ventricles which is a characteristic finding in cardiac amyloidosis.[4] Amyloid was demonstrated in the endomycardial biopsy stained with Congo red, and amyloid fibrils were also demonstrated by electron microscopy. At this time ESR was 8 mm/hr and there was no detectable paraprotein in serum or urine. A radiological skeletal survey and bone marrow examination were not performed. His cardiac failure was treated with Digoxin and diuretics and a course of Cyclophosphamide was given. However, over a two year period he became progressively disabled by diarrhoea, postural dizziness and muscular weakness. On examination his muscles were wasted and weak. All tendon reflexes were absent, and sensory testing of the extremities caused unpleasant dysasthesia. Blood pressure was 110/70 mmHg supine and 55/40 mmHg erect.

A barium enema was normal, small bowel X-ray series showed coarsening of the mucosal folds and was notable for the rapid transit time from mouth to caecum of 15 minutes. Nerve condition velocities were significantly slowed (median nerve 41 m/sec, posterior tibial nerve 36 m/sec). Heart rate on ECG monitoring did not alter with posture, respiration or valsalva manoeuvre consistent with an autonomic neuropathy.[5] Rectal biopsy showed amyloid in the submucosa and pre-treatment of the tissue sections with permanganate gave equivocal results. Haemoglobin, ESR and a biochemical screen for malabsorption were normal. Serum urea was 3.9 mmol/l (3 – 6) and protein loss in the urine was less than 0.1 gm/24 hours. Electrophoresis of serum and concentrated urine (×250) was repeated and combined with immunofixation techniques but still failed to demonstrate a paraprotein.

The cause of the diarrhoea was diagnosed as autonomic neuropathy due to amyloidosis. The postural hypotension has been improved by support stockings. The peripheral neuropathy persists and has progressed to the extent that the patient now requires a frame to aid walking. His cardiac failure remains well controlled by Digoxin and modest doses of diuretics.

DISCUSSION

Case 1 illustrates three clinical signs which are virtually pathognomonic of AL amyloidosis. These are the enlarged, indurated tongue, the shoulder pad or American footballer sign and spontaneous periorbital purpura. The purpura typically occurs after proctoscopy for a rectal biopsy and can be abbreviated to the more memorable PPPP (post proctoscopic periorbital purpura).[6]

Cases 1 and 2 are undoubtedly examples of AL amyloidosis since a circulating paraprotein was detected and there was an increased proportion of plasma cells in the bone marrow. In Case 3 a paraprotein was not detected which makes the classification of the amyloid type less certain. The detection of a paraprotein is not essential for the diagnosis of AL amyloidosis and cannot be detected in the serum in 32% of cases and in the urine in 28% of cases.[6] This patient presented with cardiac and neural involvement which are both common presentations of AL amyloidosis.[7] The normal urinary excretion of protein is unusual but can occur in 10% of cases.[6] Acquired reactive AA amyloidosis is excluded by the absence of underlying inflammatory disease. However, it is not possible to exclude a sporadic case of inherited amyloidosis, despite the lack of family history and the late age of onset (58 years).[8]

Histochemical analysis using a potassium permanganate technique[9] was unhelpful in this case. This technique is useful for identifying AA amyloid but does not distinguish AL amyloid from inherited amyloid consisting of prealbumin. Immunocytochemistry offers the prospect of a specific staining method. However, it has proved difficult to raise suitable antibodies to AL amyloid proteins because they are derived from the variable rather than the constant regions of the immunoglobulin light chains. Recently, Dalakas and co-workers have reported a series of 15 patients with amyloid polyneuropathy stained using antibodies to immunoglobulin light chains and prealbumin.[10] These patients had no family history of amyloidosis and no evidence of a plasma cell dyscrasia. In 12 of the 15 cases the amyloid protein was AL and in 3 it was prealbumin. We conclude that Case 3 is probably an example of AL amyloidosis but the classification will not be certain until these immunocytochemical techniques become more widely available.

In Cases 1 and 2 the immunoglobulin light chain belongs to the lambda (λ) class. This is consistent with previous observations that λ chains are found twice as frequently as kappa (κ) chains in AL amyloidosis, which is in contrast with myeloma not complicated by amyloidosis, in which κ chains are twice as common as λ.[6] It is not clear why λ chains should be more 'amyloidogenic' than κ chains.

A histological diagnosis is essential to confirm amyloidosis. Tissue sections which contain amyloid exhibit apple-green birefringence when stained with Congo red and examined under polarised light. Amyloid fibrils also have a characteristic appearance when examined by electron microscopy. The best site for initial biopsy is the rectum, which is positive in 80% of cases provided that submucosal tissue is obtained. The rectal biopsy in Case 1 was not deep enough to include

submucosa which is the most likely reason for the failure to detect amyloid. It may be necessary to biopsy other tissues if rectal biopsy is negative, although there is the risk of bleeding due to vessel wall infiltration or factor X deficiency which is a rare feature of AL amyloidosis.[11]

The treatment of AL amyloidosis is unsatisfactory. The most logical approach is to suppress light chain production using regimes such as melphalan and prednisone or cyclophosphamide which are of use for multiple myeloma. A prospective trial of melphalan and prednisone versus placebo showed that the nephrotic syndrome improved in a few patients but survival was not significantly changed.[12] Colchicine is effective in preventing amyloidosis in familial Mediterranean fever.[13] However, the survival of patients with AL amyloidosis is marginally worse when treated with colchicine as compared to melphalan and prednisone.[14]

Melphalan and prednisolone were given in Cases 1 and 2 and cyclophosphamide in Case 3. In the first case, amyloidosis progressed despite treatment. In Case 2 the patient died before any response to treatment could have been expected. In Case 3 the patient has remained relatively well following the course of cyclophosphamide, but it is not possible to know whether this can be attributed to the drug.

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REFERENCES

1. Glenner GG. Amyloid deposits and amyloidosis. Part 1. *New Engl J Med* 1980; **302**: 1283-92.
2. Cohen AS, Connors LH. The pathogenesis and biochemistry of amyloidosis. *J Pathol* 1987; **151**: 1-10.
3. Saraiva MJM, Costa PP, Goodman DS. Biochemical marker in familial amyloidotic polyneuropathy. *J Clin Invest* 1985; **76**: 2171-7.
4. Wizenberg TA, Jaroslaw M, Sohn YH, Samlowski WS, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the non invasive diagnosis of cardiac amyloidosis. *Am Heart J* 1982; **103**: 468-73.
5. Smith SA. Reduced sinus arrhythmia in diabetic autonomic neuropathy. *Br Med J* 1972; **285**: 1599-1600.
6. Kyle RA, Greipp PR. Amyloidosis (AL): clinical and laboratory features in 229 cases. *Mayo Clin Proc* 1983; **58**: 665-83.
7. Browning MJ, Banks RA, Tribe CR, et al. Ten years experience of an amyloid clinic — a clinicopathological survey. *Q J Med* 1986; **54**: 213-27.
8. Libbey CA, Rubinow A, Shirahama T, Deal C, Cohen AS. Familial amyloid polyneuropathy: demonstration of prealbumin in a kinship of German/English ancestry with onset in the seventh decade. *Am J Med* 1984; **76**: 18-24.
9. Wright JR, Calkins E, Humphrey RL. Potassium permanganate reaction in amyloidosis. *Lab Invest* 1977; **36**: 274-81.
10. Dalakas MC, Cunningham GG. Characterisation of amyloid deposits in biopsies of 15 patients with "sporadic" amyloid polyneuropathy. *Acta Neuropathol* (Berlin) 1986; **69**: 66-72.
11. Yood RA, Skinner M, Rubinow A, et al. Bleeding manifestations in 100 patients with amyloidosis. *JAMA* 1983; **249**: 1322-4.
12. Kyle RA, Greipp PR. Primary systemic amyloidosis. Comparison of melphalin and prednisone versus placebo. *Blood* 1978; **52**: 818-27.
13. Zenner D, Pras M, Sohar E, Modar JM, Cabili S, Grafri J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *New Engl J Med* 1986; **314**: 1001-5.
14. Kyle RA, Greipp PR, Garton JP, Gertz MA. Primary systemic amyloidosis. Comparison of melphalan/prednisone versus colchicine. *Am J Med* 1985; **79**: 708-716.