NEUROLOGICAL RARITIES

A faint in the emergency department (due to primary systemic amyloidosis neuropathy)

Michele T. M. Hu*, Carolyn M. Gabriel*, Helen J. Lachmann†, Rosalind King‡, Philip N. Hawkins† and Lionel Ginsberg‡

*National Hospital for Neurology and Neurosurgery, Queen Square, †National Amyloidosis Centre, Royal Free and University College Medical School, Rowland Hill Street, and ‡Department of Neurology, Royal Free Hospital, Pond Street, London, UK; Email: micheleh@forest hill32.fsnet.co.uk

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THE STORY

A 46-year old man was admitted as an emergency after a collapse suggestive of syncope. In fact he had been unwell for a year with malaise and fatigue, significant weight loss, progressive breathlessness and night sweats. Indeed, he had seen his family doctor 9 months previously and was found to be polycythaemic, and had had a total of seven units of blood venesected without clinical improvement. Subsequent detailed questioning elicited a history of postural dizziness and presyncope – particularly after venesection, urinary frequency, impotence, gustatory sweating, and more recently, ascending numbness and dysaesthesia of the hands and feet, poor grip strength and bilateral foot drop.

THE EXAMINATION AND INVESTIGATIONS

On examination he looked thin and unwell. An ejection systolic cardiac murmur was noted and there was a marked postural drop in systolic blood pressure (by 40–70 mmHg at various times). There was distal weakness, generalized areflexia and glove and stocking distribution loss of pin-prick, light touch and vibration sense but preserved proprioception. His ECG on admission (Fig. 1) showed a 'pseudo-infarct' pattern with poor R-wave progression, anterior ST elevation and lateral T-wave inversion, but acute myocardial infarction was excluded by normal serial troponin cardiac enzymes and a coronary angiogram was unremarkable. Routine blood tests including blood count, renal and liver function were unremarkable. Despite his normal serum albumin he had significant proteinuria (6.7 g/day) without Bence-Jones proteinuria. There was mild immune paresis with no detectable paraprotein and a normal bone marrow biopsy. An echocardiogram showed marked concentric left ventricle thickening with subvalvular outflow obstruction and an estimated gradient of 70 mmHg. At first, this and the ECG findings were thought to be consistent with hypertrophic obstructive cardiomyopathy.

Nerve conduction studies showed a mixed predominantly demyelinating sensorimotor neuropathy. Sural nerve biopsy (Fig. 2) demonstrated amyloid deposition, mainly around endoneurial blood vessels, and a predominantly axonal neuropathy. The significance of the histological findings was confirmed by radiolabelled serum amyloid P component (SAP) scintigraphy (Fig. 3; Hawkins *et al.* 1990), which

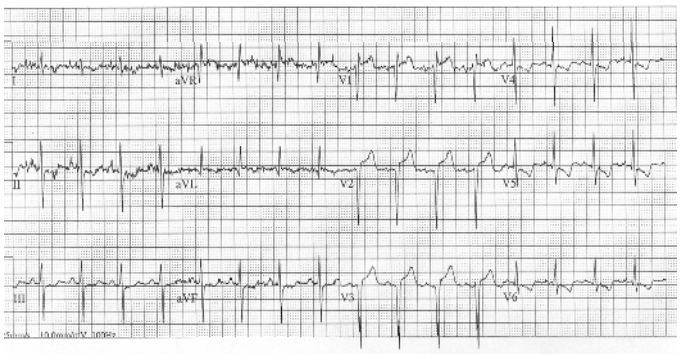


Figure 1 ECG showing a 'pseudo-infarct' pattern of poor R wave progression with anterior ST elevation and lateral T wave inversion.

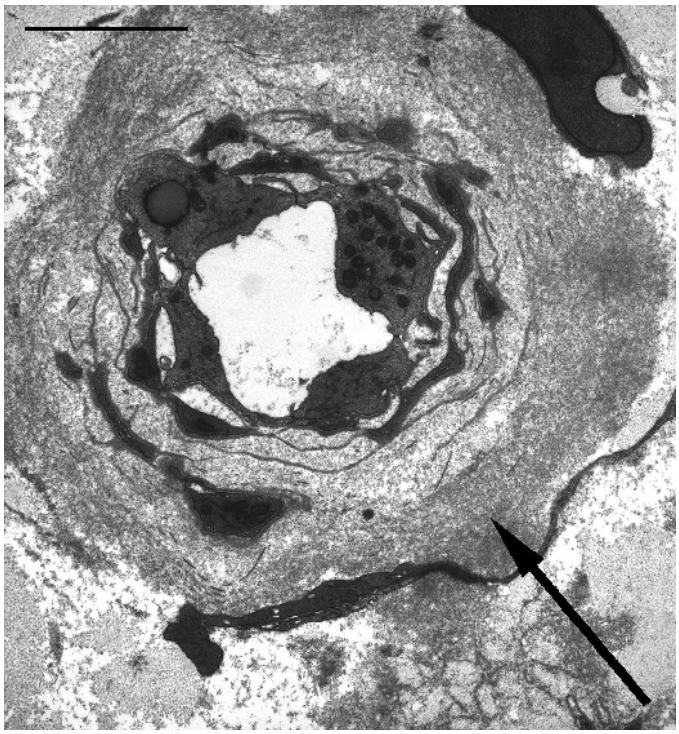


Figure 2 Electron microscopy of sural nerve biopsy showing amyloid deposition (arrow) around endoneurial blood vessel (bar = 5 μm).

showed extensive systemic amyloid deposits involving the liver, spleen, kidneys, adrenals and bone marrow, despite no abnormalities in most of these organ systems on clinical or laboratory investigation. Bone marrow involvement by amyloid on SAP scintigraphy is pathognomonic of primary AL amyloidosis, and the presence of circulating monoclonal immunoglobulin lambda light chains was confirmed by sensitive immunoassay.

The patient's postural hypotension partially responded to fludrocortisone and midodrine. Echocardiography then showed complete resolution of the outflow tract obstruction. He is presently undergoing chemotherapy (intermediate dose melphalan and prednisolone) directed towards his underlying lambda light chain secreting plasma cell dyscrasia.

PRIMARY SYSTEMIC AMYLOIDOSIS AND NEUROPATHY

The term 'amyloidosis' was first used in 1838 by the botanist M. Schleiden to describe the waxy component of plants. Waxy changes in body organs were referred to as 'lardaceous' by S. Wilks, who is credited with describing the first case of primary amyloidosis in 1856.

Amyloidosis occurs when insoluble amyloid fibrils develop from a normally soluble protein (so far nearly 20 unrelated proteins have been identified as the precursors of amyloid fibrils). Despite their different primary amino acid sequences, all amyloid proteins have similar structural properties and pathognomonic histochemical staining.

Amyloidosis may occur as a familial disorder with dominant inheritance; Portuguese, Swedish, Finnish and other varieties have been described. Non-familial amyloidosis is divided into primary amyloidosis, which occurs in the absence of other disorders (except multiple myeloma) and secondary amyloidosis in association with disorders such as chronic infection and rheumatological disease. Of these, only primary and familial amyloidosis are commonly associated with a polyneuropathy.

Primary systemic amyloidosis is a rare disorder with a prevalence of 0.9 per 100 000 population. The median age of onset is 65 years, with a male preponderance of 2 to 1. This multisystem disorder is characterized by extracellular deposition of fibrillar proteins arranged in a β-pleated sheet conformation throughout organs and tissues. The amyloid is composed of fragments of immunoglobulin light chains synthesized by

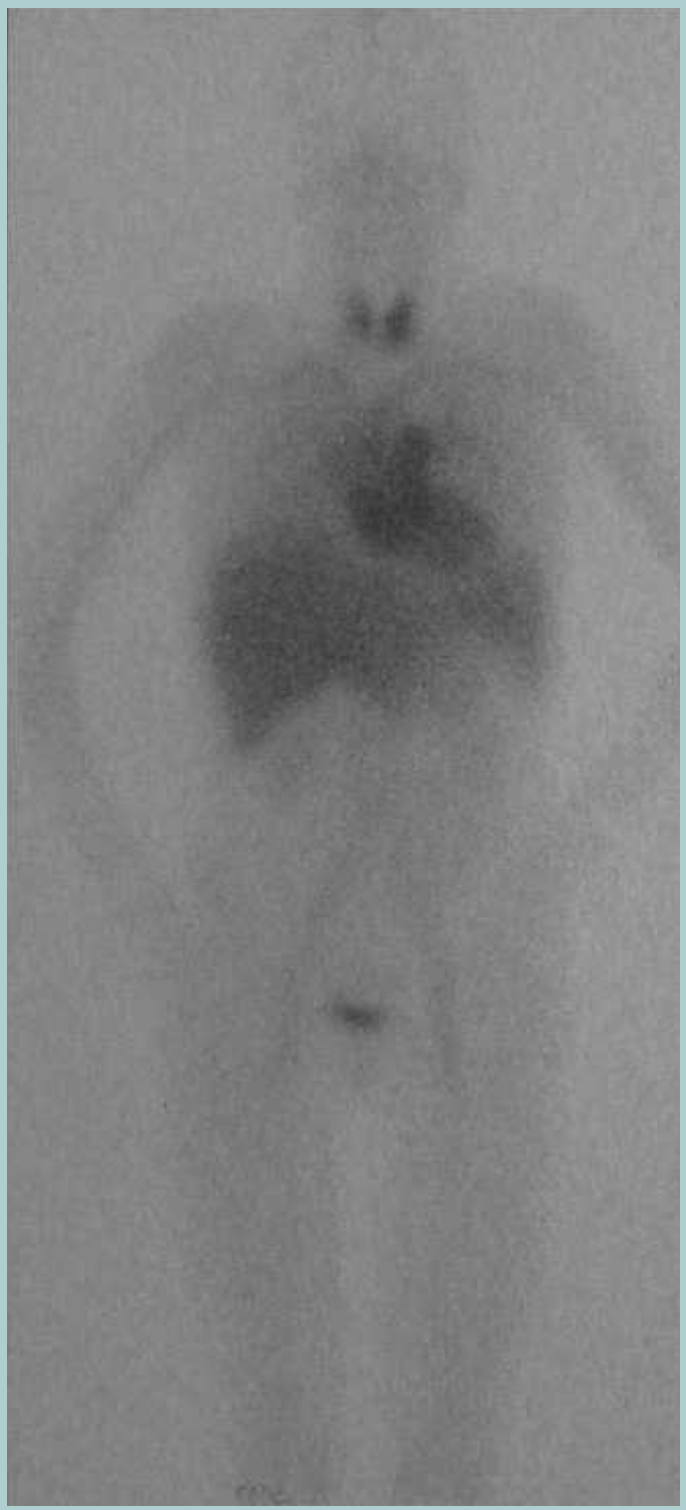
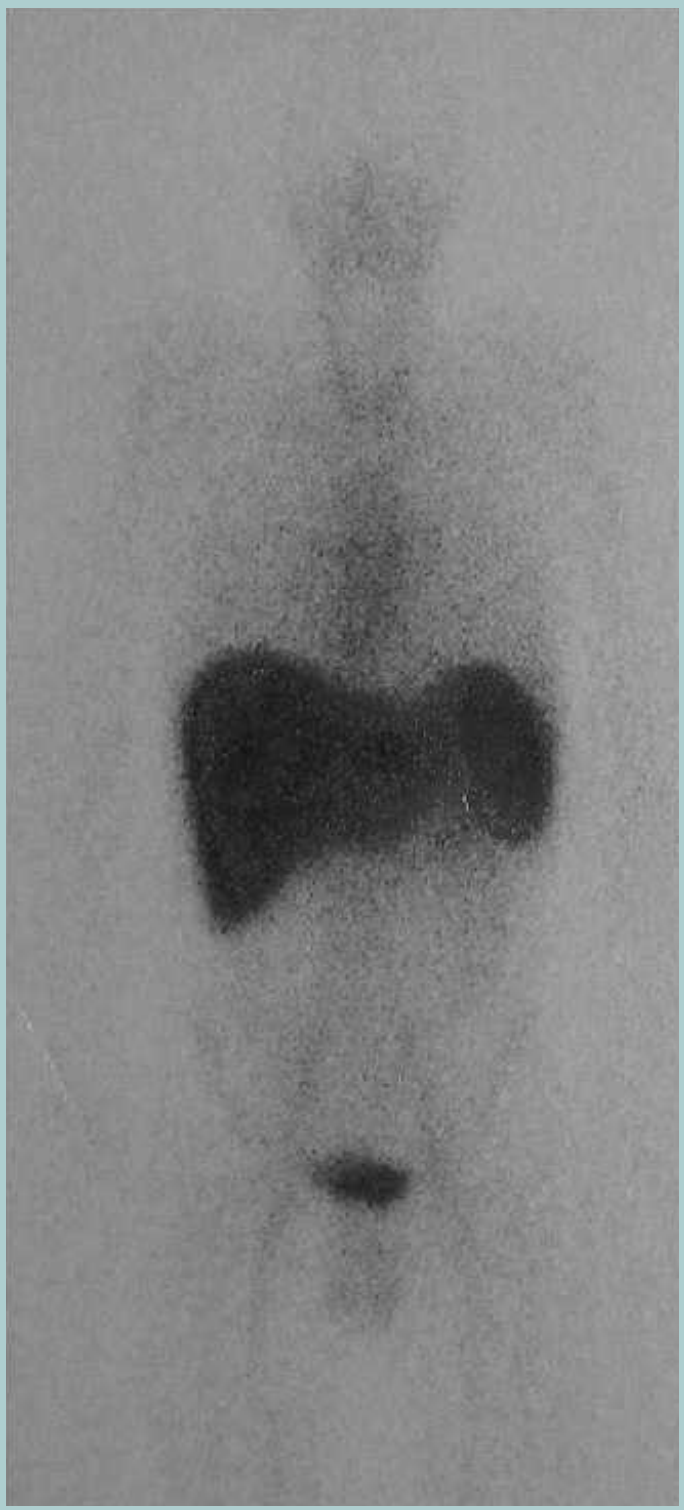


Figure 3 SAP scan in a normal person (left) showing labelled SAP uptake in the blood pool, and in our patient (right) showing abnormal uptake in liver, spleen, kidneys, adrenal glands and femoral bone marrow pathognomonic of AL amyloidosis.



clonal populations of non-proliferative cells, designated AL for amyloid light chain. Many organs are affected by AL amyloidosis which is usually widespread at diagnosis. However, the symptoms may be non-specific, and frequently the imaging and organ function tests are normal, making this condition difficult to diagnose. Furthermore, the monoclonal gammopathies that underlie AL amyloidosis are often extremely subtle, and are missed by routine serum and urinary electrophoresis in more than 20% of cases. It is not surprising therefore that our patient received six successive diagnoses – polycythaemia, cardiogenic syncope, ischaemic heart disease, hypertrophic cardiomyopathy, demyelinating polyneuropathy and amyloidosis – from as many physicians prior to the unifying diagnosis of AL amyloidosis.

Common initial symptoms are fatigue and weight loss followed by symptoms and signs related to specific organ involvement, chiefly renal disease (48%), cardiac involvement (21%) and peripheral neuropathy (9%) (Kyle *et al.* 1997). On examination hepatomegaly, macroglossia, splenomegaly and lymphadenopathy can be found. Features of diastolic and systolic dysfunction may be confirmed on echocardiography. The characteristic features of cardiac amyloid involvement are ventricular wall thickening with diastolic impairment and preserved systolic function, often mistakenly attributed to simple hypertrophy, or occasionally to hypertrophic cardiomyopathy. Left ventricular outflow obstruction has been reported rarely in amyloidosis, but this may be the result of very low systemic blood pressure. In our patient the left ventricular outflow obstruction was abolished following treatment of his systemic hypotension, a presumed haemodynamic effect. The cause of our patient's polycythaemia is unclear, but this has been described in association with AL amyloidosis (Nagasawa *et al.* 1993).

Neuropathy is the mode of presentation in 9% of patients with AL amyloidosis, the most common clinical features of which are dysautonomia and sensory polyneuropathy. There is clinical evidence of a painful peripheral neuropathy in 35% of patients at some time during the course of their illness. Paraesthesias are a frequent presenting symptom, typically beginning in the feet and spreading up the legs. Hand and arm involvement tend to occur later in the disease. With progression of the neuropathy, initial loss of pain and temperature sensation (small fibre) is followed by loss of vibration

and proprioception (large fibre). Deep tendon reflexes are diminished, with weakness tending to develop as the disease progresses (Rajkumar *et al.* 1998). In patients presenting with neuropathy, 65% have symptoms of autonomic neuropathy at diagnosis of AL amyloidosis, with a median duration of symptoms before diagnosis of 29 months. Often patients with AL amyloidosis in whom neuropathy is the dominant clinical manifestation are not diagnosed until years after the onset of symptoms (Kyle *et al.* 1997).

Common features of autonomic dysfunction include postural hypotension, impotence, gastrointestinal disturbances, pupillary abnormalities, impaired sweating and loss of bladder control. The marked degree of postural hypotension in our patient was the pivotal finding, making the diagnosis of amyloid neuropathy far more likely than other secondary causes of autonomic neuropathy (see below).

As well as a generalized neuropathy, primary amyloidosis can present with focal neurological symptoms including the carpal tunnel syndrome (CTS), although amyloidosis is an infrequent cause of CTS and will mostly be associated with other features, including weight loss, paraproteinaemia, and organ dysfunction. Amyloidosis can remain clinically localized to the carpal tunnel region, and patients on chronic haemodialysis can also develop localized amyloidosis (dialysis arthropathy) presenting as carpal tunnel syndrome (Kyle *et al.* 1989). Cranial nerve involvement is relatively uncommon in primary amyloidosis; cranial nerves III, V and VII are the most often affected.

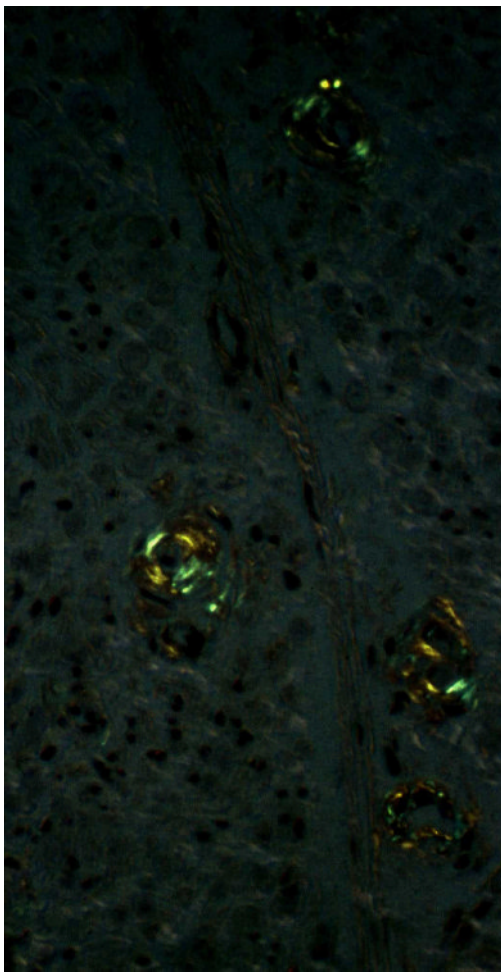


Figure 4 Sural nerve biopsy with Congo red stain, showing an apple green colour under polarized light.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Nerve conduction studies typically suggest sensorimotor axonal degeneration rather than demyelination (Rajkumar *et al.* 1998). Sensory nerve action potentials are frequently absent with mildly reduced motor amplitudes, and normal or mildly reduced conduction velocities in keeping with the degree of axonal loss. The most prominent laboratory abnormality (89%) in primary amyloidosis is the occurrence of an M monoclonal protein in the blood or urine, but often missed by routine serum and urinary electrophoresis. Pathological confirmation of amyloid deposition is required. In primary amyloidosis, it has been reported that abdominal fat biopsy is the least invasive method with an 80% yield. In patients with a prominent neuropathy, sural nerve biopsy is of high yield (86%). Deposits of amyloid fibrils can be detected near capillaries, inside nerve fascicles, and in the epineurium and perineurium (Fig. 2). There is severe axonal loss predominantly involving the small myelinated and unmyelinated fibres. Amyloid stains homogeneously pink with haematoxylin and eosin, and with Congo red stain takes on an apple green colour under polarized light (Fig. 4).

In terms of differential diagnosis, the most common cause of combined sensory polyneuropathy and dysautonomia is diabetic neuropathy. Alcohol, drugs, toxins and chronic renal failure also need to be considered, as do the Guillain–Barrè syndrome and porphyria in the acute setting. Other painful sensorimotor polyneuropathies with systemic involvement,

Consider amyloid neuropathy in patients presenting with marked postural hypotension and inadequately explained systemic symptoms

including vasculitic and paraneoplastic neuropathy, should be excluded. Familial conditions should also be considered, and of note is that not all patients with familial amyloid polyneuropathy have a family history. Familial dysautonomias usually present quite differently and at an earlier age.

PROGNOSIS AND TREATMENT

The prognosis in primary AL amyloidosis is poor, with a median survival of approximately 20 months from diagnosis (Kyle *et al.* 1997). Death is commonly caused by cardiac involvement leading to congestive cardiac failure, or by renal insufficiency. Patients with amyloid neuropathy without cardiac or renal involvement have a more favourable prognosis, with a median survival of 40 months. Therapy with oral melphalan and prednisolone prolong survival, but have no effect on the neuropathy (Kyle *et al.* 1997; Rajkumar *et al.* 1998). High dose intravenous melphalan followed by blood stem cell transplantation has been disappointing, with a much higher morbidity and mortality compared with transplantation for myeloma (Gertz *et al.* 2000).

LEARNING POINTS

- Primary systemic amyloidosis is a multisystem disorder characterized by extracellular deposition of fibrillar proteins throughout many organs and tissues of the body.
- Symptoms are often non-specific and the routine tests normal. A diagnostic delay of over 2 years from symptom onset is not uncommon.
- Frequent initial symptoms are fatigue and weight loss, with other symptoms and signs related to cardiac involvement, renal impairment and peripheral neuropathy. Organ involvement is usually extensive at diagnosis.
- Median survival is 20 months from diagnosis, with death due to congestive cardiac failure, arrhythmias and renal impairment.
- Consider amyloid neuropathy in patients presenting with marked postural hypotension and inadequately explained systemic symptoms.

Primary AL amyloid was the subject of a recent interesting clinico-pathological conference in *Practical Neurology* (December 2003).

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