

**Title**

AL amyloidosis presenting with isolated lumbosacral radiculoplexus neuropathy

**Authors and affiliations**

Roberto Bellanti<sup>1</sup>, Mkael Symmonds<sup>1,2</sup>, Rajat Chowdhury<sup>3</sup>, Monika Hofer<sup>1,4</sup>, Simon Rinaldi<sup>1</sup>

1. Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
2. Department of Clinical Neurophysiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
3. Department of Musculoskeletal Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
4. Department of Neuropathology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

**Corresponding author**

Associate Professor Simon Rinaldi  
Nuffield Department of Clinical Neurosciences  
University of Oxford  
Oxford, UK  
Phone: +44 (0)1865 231912  
Email: [simon.rinaldi@nhs.net](mailto:simon.rinaldi@nhs.net)

**Word count:** 1500

**Number of references:** 6

**Number of figures:** 2

**Number of tables:** 0

## **Abstract**

A 45-year-old man presented with an isolated sciatic mononeuropathy which then evolved into a lumbosacral radiculoplexus neuropathy. His initial symptoms included lower limb pain, sensory disturbance and later weakness, without autonomic dysfunction. Neurophysiology suggested a postganglionic neuropathy, MRI and ultrasound of the thighs demonstrated thickening of the right sciatic nerve, and CSF analysis showed albumino-cytological dissociation. FDG PET was unremarkable. He then developed orthostatic symptoms and urinary disturbance, and was found to have an IgM paraprotein. Fat aspirate, cardiac and whole-body imaging did not show amyloid deposition, and genetic testing for transthyretin amyloidosis was negative. A bone marrow biopsy was also unremarkable. However, neuropathology review of a proximal, fascicular nerve biopsy identified a lambda chain-restricted plasma cell population with positive Congo red staining, leading to a diagnosis of peripheral nerve restricted AL amyloidosis. We discuss the diagnostic approach to this case from the perspectives of neurology, neurophysiology, radiology and neuropathology.

## **Case description**

A 45-year-old right-handed male management consultant presented with a one-year history of progressive pain and hyperaesthesia in his lower limbs (initially lateral aspect of his left thigh and medial side of the knee). He denied back pain, sphincter disturbance or unsteadiness. His medical and family history were unremarkable. Following an initial tele-medicine diagnosis of meralgia paraesthetica, he developed right foot weakness over the subsequent eight months. At a subsequent in-person review, examination revealed an absent right ankle jerk and reduced pinprick sensation over the lateral aspect of both thighs and medial side of the knees. Initial investigations demonstrated a mildly raised creatin kinase (CK 305, 30-200 IU/L), lactate dehydrogenase (LDH 258, 90-236 IU/L), and IgM 2.97 (0.4-2.5 g/L) levels, without evidence of a paraprotein on serum protein electrophoresis, and positive anti-GM1 antibodies (1:800). MRI of the lumbosacral spine was unremarkable. Electrophysiology showed abnormalities in the right leg, comprising an absent sural and reduced superficial peroneal sensory nerve action potentials (SNAPs), and attenuated compound muscle action potential (CMAP) amplitudes from both peroneal (extensor digitorum brevis) and tibial (abductor hallucis) innervated muscles. Abnormal sensory responses indicated a postganglionic lesion, with involvement of both peroneal and tibial responses localising to the sciatic nerve or lumbosacral plexus. Needle Electromyography (EMG) identified fibrillation potentials (indicating active denervation) and enlarged irregular motor unit action potentials (indicating chronic denervation) in right tibialis anterior and gastrocnemius, with normal appearances of hamstrings and gluteii, indicate a likely sciatic neuropathy. MRI of the thighs showed diffuse

thickening of the right sciatic nerve, confirmed by ultrasound (USS). Both MRI and USS were reported as consistent with a probable inflammatory neuropathy. Cerebrospinal fluid (CSF) analysis revealed high protein (1.12 g/L), normal white cell count, and no neoplastic cells. FDG PET was unremarkable. Over the next six months, his symptoms progressed with proximal lower limb weakness, erectile dysfunction, orthostatic hypotension and urinary retention. At this stage, amyloidosis was suspected. Repeat nerve conduction studies showed a progression of abnormalities in the right leg, with now absent peroneal and tibial distal sensory and motor responses. There were also subtle abnormalities from the left leg with a mildly prolonged H-reflex (the electrophysiological equivalent of the ankle jerk) and F wave responses (which assess proximal motor conduction), but not in the range seen in demyelinating disorder. EMG showed in addition to the previous right-sided abnormalities, active on early chronic neurogenic changes in the L1-3 myotomes. This suggested a patchy, asymmetrical bilateral lumbosacral plexopathy or polyneuropathy. MRI pelvis and lower limbs demonstrated bilateral lumbosacral plexopathy with marked enlargement of the right sciatic nerve fascicles in the mid posterior thigh extending to the popliteal fossa. S1 roots, femoral nerves and obturator nerves were bilaterally enlarged [Figure 1]. A small IgM lambda paraprotein was found on serum protein electrophoresis (SPE) with immunofixation. Serum Amyloid P component (SAP) scan, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scan, fat aspirate and echocardiogram were negative for amyloid deposition. Transthyretin (TTR) and Next Generation Sequencing (NGS) amyloid panels were negative. Bone Marrow Aspirate and Trephine (BMAT) showed no evidence of a plasma cell neoplasm or amyloid deposition. Right sciatic fascicular nerve biopsy was initially reported by musculoskeletal pathologists, unaware of the likely differential, as consistent with an intraneural neurofibroma, based on positive S100 and EMA (Epithelial Membrane Antigen) staining. Following neuropathology review, further testing was performed, revealing a lambda chain-restricted plasma cell

population with extensive Congo red positive deposits and apple green birefringence [Figure 2]. In light of these findings, a diagnosis of AL amyloid neuropathy was made. The presence of clonal plasma cells in the nerve suggested a neoplastic aetiology and he was treated with rituximab and bendamustine (six cycles over six months), which led to improvement of the sensory disturbance and no further progression of the overall neurological picture.

## **Discussion**

Amyloid light chain (AL) is caused by the deposition of unstable free immunoglobulin light chains secreted by bone marrow-residing plasma cell (PC) clones, usually in the context of a haematological dyscrasia. Light chains deposit in organs and tissues where they cause progressive dysfunction. Typically, AL amyloidosis involves the kidneys, gastrointestinal tract, heart, liver and nervous system. Infiltration of the cardiac conduction system causes arrhythmias which can be fatal and represent the main cause of death in patients with AL amyloidosis. (1) Isolated peripheral nervous system (PNS) involvement in AL amyloid is rare and only a few cases have been reported in the literature. Previously described PNS locations include sciatic nerve, cervical roots and brachial plexus, and only two cases of isolated lumbosacral plexopathy have been reported to date. (2,3)

In our patient, FDG PET, SAP scan, DPD scan, fat aspirate and echocardiogram were all unremarkable, and the lambda light chain-restricted plasma cell population was only found upon histological review by neuropathologists. Kappa and lambda in situ hybridisation (ISH) labels plasma cells expressing kappa and lambda cells respectively, and positive Congo red staining with apple green birefringence is pathognomonic for AL amyloidosis. However, the presence of clonal plasma cells in the nerve is

unusual and suggests direct malignant infiltration as opposed to non-neoplastic AL amyloidosis, where no intraneural plasma cells should be found. This might explain why the presentation was focal unlike more typical AL amyloid cases which tend to have diffuse, often PET-evident visceral involvement. The combination bendamustine-rituximab is effective in the treatment of B cell lymphoproliferative disorders, can penetrate blood-brain and blood-nerve barrier, and has been reported to be effective in CNS lymphoma as well as neurolymphomatosis.(4)

The addition of immunofixation (IF) to serum protein electrophoresis increases sensitivity and allows typing of the paraprotein. (5) SPE without IF quantifies the paraprotein but is not sufficiently sensitive in low-grade lymphomas, monoclonal gammopathies of unknown significance (MGUS) or in those cases where the paraprotein causes AL amyloidosis. As most clinical laboratories do not routinely perform immunofixation, it is essential to specify that AL amyloidosis is suspected as the paraprotein will most likely be missed with SPE alone.

Our patient's mild CK elevation was likely indicative of mild neurogenic muscle damage and not due to a primary myopathy. Anti-GM1 antibodies were clearly incidental in retrospect, as the clinical and electrophysiological findings were not consistent with Guillain-Barré syndrome or multifocal motor neuropathy (MMN), and the CSF albumin-cytological dissociation was in keeping with nerve root involvement rather than a sign of a primarily inflammatory neuropathy such as CIDP. Nerve conduction studies showed a predominantly axonal pattern of abnormalities, with reduced or absent action potentials (SNAPs and CMAPs). Mild slowing of distal or proximal (F-wave) conduction velocity is often associated with axonal damage due to loss of the largest and fastest conducting nerve fibres, and also be seen in nodal/paranodal neuropathies; demyelinating lesions typically associate with significantly greater slowing, often disproportionate to reductions in CMAP

amplitude, with associated temporal dispersion and delayed distal latencies, which were not present in this case. The finding of diffuse nerve thickening on MRI and ultrasound is also non-specific, and can indicate a wide differential of nerve diseases including inflammatory, infiltrative, infective, and genetic neuropathies (where the presence of thickened nerve roots may occur in genetic demyelinating neuropathies such as CMT1A). Imaging should always therefore be interpreted in the appropriate clinical context.

SAP imaging is only available at the National Amyloid Centre, to which our patient was referred. SAP scanning quantifies serum amyloid P component deposition in the body and is useful in assessing response to therapies. However, it is poorly sensitive for the detection of peripheral nerve AL amyloid and does not provide adequate information about organs in constant motion such as the heart. DPD imaging is used to diagnose cardiac amyloidosis, and its sensitivity and specificity are higher in hereditary transthyretin amyloidosis (ATTR) compared with AL amyloid.

Ultimately, histopathology remains pivotal for the diagnosis of AL amyloidosis. (6) Although non-specific, imaging and nerve conduction studies can guide selection of which nerve to biopsy. Our patient's biopsy was performed in a special peripheral nerve surgical unit, and the right sciatic nerve was chosen on the basis of MRI, USS and neurophysiology findings, which suggested biopsy of more distal nerves was likely to only reveal non-specific axonal degeneration. Occasionally, distal biopsies can find AL amyloid even when imaging shows proximal involvement. Amyloid deposits are typically found within the endoneurium, perineurium, and epineurium, often with moderate to severe axonal loss, active degeneration and, less frequently, evidence of chronic inflammatory cell infiltrates. In the absence of apple green birefringence, and if diagnosis remains uncertain, a concomitant muscle biopsy can increase the diagnostic yield by

demonstrating amyloid deposition and should be considered on an individual patient basis.

### **Key points**

1. If AL amyloidosis is suspected, immunofixation must be requested in addition to serum protein electrophoresis, as SPE alone is not sufficiently sensitive.
2. MRI and neurophysiology findings are often non-specific, and nerve biopsy may be required if the diagnosis remains uncertain following less invasive investigations.
3. Positive Congo red staining with apple green birefringence on biopsy is pathognomonic for AL amyloidosis. The presence of a clonal plasma cell population in the nerve suggests a malignant lymphoproliferative disorder.

### **Further reading**

1. Al Hamed R, Bazarbachi AH, Bazarbachi A, Malard F, Harousseau JL, Mohty M. Comprehensive Review of AL amyloidosis: some practical recommendations. *Blood Cancer J.* 2021 May 18;11(5):1-13.
2. Carroll AS, Lunn MPT. Paraproteinaemic neuropathy: MGUS and beyond. *Pract Neurol.* 2021 Dec;21(6):492-503.
3. Kapoor M, Rossor AM, Jaunmuktane Z, Lunn MPT, Reilly MM. Diagnosis of amyloid neuropathy. *Pract Neurol.* 2019 Jun;19(3):250-8.

### **Competing interests**

None declared



## **Acknowledgements**

None

## **Contributors**

RB and SR wrote the original draft of the manuscript. MS, RC and MH contributed to subsequent drafts and revisions. All authors approved the final version.

## **Funding**

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

## **Ethical approval information**

Not applicable

## **Patient consent for publication**

Consent directly obtained from patient

## **Data sharing statement**

No data are available

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## Figure legends

**Figure 1.** MRI pelvis and lower limbs. Bilateral asymmetrical polyneuropathy involving the entire lumbosacral plexus. Involvement is most marked in the right sciatic nerve in the mid posterior thigh extending to the popliteal fossa.

**Figure 2.** Fascicular biopsy of the right sciatic nerve. (A) Extensive Congo red positive deposits (arrow), with apple green birefringence when polarised (see \*, inset). (B, C) Plasma cells predominantly expressing lambda light chain consistent with lambda light chain-restricted plasma cell population. (B) Lambda in situ hybridisation in situ hybridization (ISH). (C) Kappa ISH.