Pathology (■ 2016) ■(■), pp. 1–3

CORRESPONDENCE

Localised SAA amyloidosis with intra-axonal intra-myelin amyloid deposits

Sir,

Neuropathy occurs in certain forms of systemic amyloidosis. The most common cause of amyloid neuropathy (AN) is immunoglobulin light-chain (AL) amyloidosis.[1] In addition, familial forms of amyloidoses such as transthyretin (ATTR), apolipoprotein AI (AApoAI) and gelsolin (AGel) can result in AN.[1] Within the nerve, amyloid deposits are restricted to the connective tissues (endoneurium, perineurium, and epineurium) and blood vessels (arterioles and capillaries).[1,2] Localised amyloid neuropathy of AA type is not reported in the literature. We report a case of AA amyloidosis where the amyloid deposits were localised exclusively within the axons and myelin sheaths. The connective tissue and vascular compartments were devoid of amyloid deposits.

A 28-year-old man presented with easy fatigability, passage of frothy urine, early morning facial puffiness and abdominal distension for 1 year. There was no associated flank pain, mass, haematuria or reduced urine output. He also had progressive distal weakness of the right upper limb and left lower limb for 4 months. There was no associated pain, numbness, paraesthesia or autonomic dysfunction. There was no family history of any connective tissue disease or amyloidosis. General examination revealed pallor and anasarca. Neurological examination showed a thickened ulnar nerve. Motor strength was 4/5 in the right elbow extensors, 0/5 in the right wrist extensors and 0/5 on dorsiflexion of the left foot. Deep tendon reflexes were 1+ in both the biceps and triceps but absent in the left ankle. No signs of autonomic involvement were evident. Nerve conduction studies were compatible with an axonal sensorimotor polyneuropathy. Investigations revealed nephrotic range proteinuria. Serum and urine protein electrophoresis failed to reveal any M band. Other investigations including serum free light chain assay, ANA, ANCA, HIV, HbsAg, anti-HCV, and split skin smear for leprosy were negative. A duodenal biopsy and abdominal fat pad aspirate were negative for amyloid deposits.

The overall clinical impression was systemic amyloidosis and a renal biopsy was performed. The conventional and special stains (including Congo red) performed on the renal biopsy were suggestive of minimal change disease (MCD). Immunofluorescence studies (IgG, IgA, IgM, C3, C1q, fibrinogen, kappa and lambda light chains) were negative. Electron microscopic examination confirmed MCD with effacement of podocyte foot processes and absence of amyloid deposits (Fig. 2D).

Since the peripheral neuropathy was not explained, a sural nerve biopsy was performed (Fig. 1 and 2). The biopsy revealed nine fascicles. Pale amorphous acellular deposits were observed exclusively within the myelin sheaths and the axons on paraffin and resin sections stained with H&E and toluidine blue, respectively (Fig. 1A,B). These deposits were congophilic (Fig. 1C) and exhibited apple green birefringence under polarised light. The deposits were also brilliantly highlighted under fluorescent light (Fig. 2A,B). Thus, the deposits were confirmed to be amyloid. Subsequent subtyping of the deposits using SAA, kappa and lambda light chain immunostains revealed immunoreactivity only for SAA (Fig. 2C). The connective tissue and vascular compartments, however, failed to reveal any amyloid deposits (Fig. 1D). A final diagnosis of SAA amyloid neuropathy restricted to the axons and myelin sheaths with sparing of connective tissue compartments was made.

The patient was subsequently worked-up for systemic SAA amyloidosis and its complications. The serum SAA levels were normal (7 mg/L). Contrast-enhanced computed tomography (CECT) of chest and abdomen and whole body positron emission computed tomography (PET-CT) did not reveal any abnormality. Pulmonary function tests were normal, 2D echocardiography was normal, troponin I was 0.02 ng/mL (normal range 0–0.02 ng/mL) and serum NT-Pro-BNP levels were 40.2 pg/mL (normal range 0–100 pg/mL). Thus, the SAA amyloidosis was confirmed to be localised within the peripheral nerves and no underlying aetiology was identified. His proteinuria improved after a course of corticosteroids but the neuropathic symptoms continued to worsen. He is on regular physiotherapy to prevent contractures.

The amyloidoses are disorders of protein misfolding resulting in protein aggregation and formation of insoluble abnormal fibrils.[3] Amyloid deposits in AA amyloidosis are always systemic and are chiefly derived from the precursor serum amyloid A (SAA) protein.[4] SAA belongs to the family of proteins that include SAA1, SAA2, and SAA4. SAA1 and 2 are acute phase reactants synthesised within the hepatocytes in response to transcriptional stimuli from various proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumour necrosis factor alpha.[5] AA amyloidosis can occasionally be the result of familial Mediterranean fever and other forms of periodic fever. The distribution of AA amyloid deposits is relatively constant and observed in sites such as subcutaneous adipose tissue, gastrointestinal mucosa, and kidneys.[4] The variable organ distribution is attributed to the variation in SAA cleavage sites (dependent on presence or absence of certain polymorphisms) and the local milieu (balance between the amyloidogenic and non-amyloidogenic factors).[6] Peripheral, cranial and autonomic nervous system involvement by AA amyloidosis is extremely uncommon. To the best of our knowledge, there are only two unequivocal reports of AA amyloid neuropathy in the literature.[7,8]

Our case is unique in several aspects. Firstly, this is the first reported case of localised AA amyloidosis (limited only to the peripheral nerves). Secondly, this is the first case of amyloidosis where the deposits were exclusively within the axons and myelin sheath (sparing the vascular and extracellular connective tissue compartments). Thirdly, this is the first case of localised AA amyloid neuropathy in association with renal MCD.

Although most often AA amyloidosis results secondary to an underlying chronic disease, a considerable number of patients do not have any underlying disorder.[9] Thus, the index case is not an exception. Moreover, improvement in the nephrotic syndrome and worsening of peripheral neuropathy

Print ISSN 0031-3025/Online ISSN 1465-3931

Please cite this article in press as: Gaspar BL, et al., Localised SAA amyloidosis with intra-axonal intra-myelin amyloid deposits, Pathology (2016), http://dx.doi.org/10.1016/j.pathol.2016.08.018