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Mass spectrometry analysis reveals non-mutated ApoA1 lumbosacral radiculoplexus amyloidoma

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Abstract

Introduction—Rarely, amyloidosis presents as a focal, macroscopic lesion involving peripheral neural tissues (amyloidoma). In all known reported cases, peripheral nerve amyloidomas have immunoglobulin light chain fibril composition and occurred in the context of paraproteinemia.

Methods—A 46 y.o. man presented with progressive insidious onset right lumbosacral radiculoplexus neuropathy without paraproteinemia. MRI-targeted fascicular nerve biopsy was performed on an enlarged sciatic nerve after earlier distal fibular nerve biopsy was nondiagnostic. Laser dissected mass spectroscopy of the discovered amyloid protein was performed after immunohistochemistry failed to identify the specific amyloid protein. Complete gene sequencing of ApoA1 was performed.

Results—Only wild type ApoA1 amyloid was found in the congophilic component in the nerve.

Discussion—The case highlights the utility of MRI guided fascicular nerve biopsy combined with laser dissected mass spectrometric analysis. Importantly, the case expands the known causes of amyloidomas to include wild type ApoA1.

Keywords

Amyloidoma; Apolipoprotein A1; Peripheral neuropathy; Amyloidogenesis; Mass spectrometry

Introduction

Most commonly, amyloidosis of peripheral neural tissues is pathologically characterized by diffuse, microscopic, predominantly endoneurial deposition of amyloid protein.^{1,2} The dorsal roots and autonomic ganglia typically show early involvement, but deposition can extend to all nerve segments and nerve fiber types.^{3,4} These pathologic involvements most commonly manifest clinically as a length-dependent, sensory before motor neuropathy with prominent dysautonomia. Rarely, focal macroscopic deposition of amyloid, i.e. amyloidoma, can involve peripheral neural tissues, usually originating from vertebral bodies^{5,6} or within the Gasserian ganglia.⁷ There are very few reported cases of amyloidomas arising within peripheral nerve tissues of the extremities.⁸⁻¹¹ In all amyloidomas reported to date, amyloid fibrils are composed of immunoglobulin light chains and have arisen in the context of known systemic monoclonal gammopathy.

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Amyloid deposits comprised of non-variant protein are known to occur in chronic inflammatory conditions (secondary amyloidosis AA), where deposits are composed of serum protein A (SAA), and in senile systemic amyloidosis, where deposits are composed primarily of wild type transthyretin. Peripheral neural tissue involvement in such conditions is not described.¹² All known cases of peripheral nervous system amyloidosis have occurred in the context of plasma cell dyscrasia (i.e. primary light chain amyloidosis AL) or inherited mutations of transthyretin, gelsolin, or ApoA1.¹³ Autonomic neuropathy has been reported in hereditary fibrinogen amyloidosis, but it has not been confirmed histopathologically in peripheral nerve.^{14,15} ApoA1 is by far the rarest of known causes of amyloid associated neuropathy. It invariably presents with kidney involvement as well as cardiac and cutaneous amyloid deposits.^{16,17} In amyloidosis, the amyloid fibrils are associated with other proteins, including heparan sulphate proteoglycan, laminin, collagen IV, serum amyloid P, and apolipoprotein E.¹²

Localized macroscopic amyloid deposition seen with amyloidomas directs attention to unsettled pathologic implications of amyloidogenesis. Specifically, whether amyloidomas represent a localized primary overwhelming of normal protein recycling processes versus a macroscopic “tombstone” remnant of a more primary pathologic process is unclear.¹⁸ The tendency for distribution of amyloid in certain tissues, including the peripheral nervous system, is poorly understood and may relate to the balance between each tissue’s ability to clear amyloidogenic proteins relative to its tendency to generate or accumulate them.¹⁶ Amyloidomas provide an extreme example of these issues.

We report a patient with lumbosacral radiculoplexus amyloidoma in which we utilized recently described mass spectrometry analysis¹⁹ to identify ApoA1 as the amyloid fibril of origin without systemic markers of paraproteinemia.

Case report

A 46 year-old right handed man had 5 years of slowly progressive right lower extremity symptoms and was previously well without history of neuromuscular disease. His first symptoms consisted of loss of feeling and tingling of the right lateral foot and leg. Six months subsequently he became aware of a slapping of his right foot as he walked. He then developed frequent cramping of his right calf and hamstrings which would wake him from sleep with occasional paroxysms of shock-like pain radiating from the buttock to the lower leg. The dorsiflexion strength of the right ankle progressively decreased over the following year to the point he was not able to ankle dorsiflex against gravity. He then gradually became aware of plantar flexion weakness such that he found it difficult to lift all his weight with that single ankle and foot against gravity. He noticed atrophy in his right buttock, posterior thigh, and leg. He was without symptoms in other extremities and denied sweat, erectile or orthostatic symptoms. He had an identical twin brother who was healthy, and there was no known family history of neuropathy, amyloidosis, or plasma cell dyscrasia.

MRI of the lumbosacral spine, lumbosacral plexus, and distal nerves showed marked enlargement and T2 hyperintensity of the right L4 through S3 segments extending proximally to the roots (figure 1), which were consistent with a right lumbosacral radiculoplexus neuropathy involving the L4-S3 segments, lumbosacral plexus, sciatic and femoral nerves. No contrast enhancement was seen after gadolinium administration. Denervation edema and atrophy were seen in the gluteus maximus, the posterior thigh compartment, and the abductor muscles of the right thigh with trace adductor involvement. No abnormalities were detected on the left.

Nerve conduction studies performed 2 years from symptom onset showed a normal right tibial compound muscle action potential (CMAP), reduced right sural sensory nerve action

potential (SNAP), absent right superficial fibular SNAP, and absent right fibular CMAP. The F-wave latency was prolonged in the right tibial nerve. Needle electromyography showed fibrillation potentials in the right tibialis anterior, and no motor unit potentials (MUPs) were recruited. Fibrillation potentials and large MUPs were noted in the right medial gastrocnemius, short head of the biceps, gluteus maximus, and gluteus medius. Vastus medialis needle examination was normal. Biopsy of the right fibular nerve at the level of the knee showed moderate, generalized axonal loss with Wallerian-degeneration but indicated no specific etiology for the neuropathic process.

Based on imaging characteristics, a working diagnosis of hypertrophic inflammatory neuropathy was made, and a course of 2 grams (grams/kg) of intravenous immunoglobulin was initiated in divided doses over five days, followed one month later by a second identical course. No benefit was appreciated. He was referred for subspecialty peripheral nerve consultation in evaluation of this problem.

On neurologic examination 5 years from symptom onset, he had normal mental status, speech, and cranial nerve exam. Motor and sensory examination of the upper extremities and the left leg was unremarkable. In the right leg, he had marked atrophy of the buttocks, hamstrings, tibialis anterior, and calf muscles. He had MRC grade 4 strength of hip abduction sparing hip flexion, grade 4 strength of knee flexion, normal strength of knee extension and adduction, without movement in ankle dorsiflexion, toe extension, and eversion, and grade 3 strength of ankle inversion, toe flexion, and plantar flexion. Tendon stretch reflexes were mildly reduced at the right patellar tendon, moderately reduced at the right Achilles tendon and were normal elsewhere. Sensory examination demonstrated panmodal sensory loss of the dorsolateral foot and lower leg.

Serum and urine protein electrophoresis, immunofixation, light chain analyses, and plasma cell flow cytometry were normal and were repeatedly so on annual examination over three years. Other normal studies included a complete cell count and differential, electrolyte panel, serum antineuronal antibody panel, sedimentation rate, rheumatologic markers (ANCA, RF, CCP antibodies), ganglioside antibody panel, PMP-22 gene analysis, serum Lyme disease Western blot, TSH, ACE level, renal and liver function studies, creatine kinase, vitamin B12, and folate levels. Cerebrospinal fluid showed protein of 36.6mg/dL, glucose of 64, normal cell count and cytology, and negative Lyme polymerase chain reaction. Congo red staining of subcutaneous fat aspirate showed no amyloid deposition. Peripheral blood, bone marrow aspirate, and biopsy of the iliac crest showed no morphologic or immunophenotypic findings of involvement by a plasma cell proliferative disorder, and bone marrow was normocellular (50%) with normal trilineage hematopoiesis. F-18 FDG PET/CT scan was performed from the orbits through the upper thighs on two occasions and showed no abnormal foci of FDG accumulation to suggest plasmacytoma.

A second nerve biopsy using a targeted fascicular approach facilitated by the described MRI imaging was obtained from the tibial division of the sciatic nerve just distal to the sciatic notch. Intraoperatively, the sciatic nerve appeared enlarged in a fusiform fashion over about 6cm, tapering distally. Teased fiber analysis showed only unclassifiable fibers with large amounts of adherent, flocculent material. Semithin sections stained with methylene blue demonstrated severely decreased myelinated fiber density in a diffuse pattern, and only occasional, thinly myelinated fibers were seen. A large collection of subperineurial mononuclear cells was seen on paraffin sections. Amorphous, acellular material was seen diffusely throughout the endoneurium and perineurium. It was Congo red positive and showed apple green birefringence with polarized light (figure 2). Numerous mononuclear cells containing intracellular inclusions with a Maltese cross pattern of birefringence were present throughout the endoneurium. Electron microscopy together with

immunohistochemical staining (which included S100, EMA, KP-1, CD 163, and CD11C preparations) demonstrated many of the cells to be macrophages, each with a single, large intracellular aggregate of fibrous material arranged in a starburst-like pattern (figure 3). Some starburst aggregates were partially extracellular and were closely associated with macrophages or Schwann cells; others were extracellular and were apparently remote from any mononuclear cell. Immunohistochemical staining of the congophilic material was indeterminate for specific type, including preparations for transthyretin, IgG kappa, and IgG lambda. Serum amyloid protein (SAP) and ApoE staining were present.

To understand the protein composition of the amyloid deposit we isolated the proteins by laser microdissection, and after trypsin digestion we did liquid chromatography electrospray tandem mass spectrometry analysis (LMD-MS).¹⁷ The data was queried using three different algorithms (Mascot, Sequest and X!Tandem); the results were assigned peptide and protein probability scores and displayed using Scaffold (Proteome Software, Portland, OR). All known amyloid proteins and their associated proteins were queried. Only ApoA1 and serum SAP without other known amyloid or amyloid associated proteins were found. With the result, ApoA1 DNA mutations were sought, and complete sequencing of the entire open reading frame of the ApoA1 gene was found to be normal.

Discussion

This patient had clinical imaging, intraoperative, and histologic findings of a peripheral nerve amyloidoma, with a previously undescribed composition of amyloid, consisting of isolated wild type ApoA1. Biopsy of the distal fibular nerve failed to identify the amyloid protein, whereas targeted proximal fascicular biopsy identified the pathologic amyloid component. There were no systemic markers of primary AL-amyloidosis by serial serologic, urine or bone marrow analyses or by nerve amyloid spectrometric-analysis. This case highlights the clinical utility of targeted fascicular nerve biopsy and laser microdissected mass spectrometry (LMD-MS) analysis in identifying and characterizing the composition of amyloid deposits. The use of immunohistochemistry to identify amyloid type was problematic in this patient's nerve, as has been described previously.^{19,20} Through proteomic analysis of his biopsy, including evaluation for all known amyloid-associated and amyloidogenic proteins, ApoA1 was the identified amyloid protein. In this case no mutation was found in the ApoA1 gene. The occurrence of a non-mutated accumulation of ApoA1 to our knowledge has not been reported in nerve amyloidosis.

ApoA1 amyloidosis is the rarest of known inheritable causes of peripheral nerve amyloidosis. Only an arginine for glycine substitution at position 26 (Gly26Arg) in the ApoA1 gene on chromosome 11 (11q23) has been found to be associated with neuropathy.²¹ All instances of ApoA1 amyloidosis have been seen in heterozygotes in whom both wild type and variant ApoA1 are found in serum. The amyloid deposits, however, contain only the amino terminal 83-93 amino acid residues of the variant protein.^{13,22,23} This is in contrast to familial transthyretin (TTR) amyloidosis, in which deposits contain 35-40% wild type TTR, a proportion which increases after orthotopic liver transplant.²⁴⁻²⁸ Non-variant TTR amyloid accumulation in isolation is reported in senile amyloidosis with heart failure.²⁹

ApoA1 is produced mainly in the liver and intestine and is the major component of high density lipoprotein. It functions as both a cofactor for lecithin cholesterol acyltransferase and as a cholesterol transporter. In all cases of variant ApoA1 amyloidosis, mutations are thought to result in reconfiguration of the protein to the predominant B-helical structure requisite for formation of amyloid fibrils. Full length ApoA1 contains both alpha-helical and non-helical structure, as well as short sections of beta-pleated sheet.³⁰ Conditions which have been shown to impart wild type ApoA1 with greater amyloidogenic potential include

simple local displacement of ApoA1 from its associated lipoprotein particles²² and methionine ApoA1 oxidation.³¹ Both of these processes are promoted by the inflammatory milieu, which may be the unifying characteristic of the few previous reports of wild-type ApoA1 amyloid deposition in atherosclerotic plaques,^{23,32,33} in pulmonary vasculature of aging dogs,³⁴ and in the knee meniscus of patients undergoing surgery for degenerative arthropathy.³⁵

A striking pathologic feature in our case was the abundance of birefringent macrophage inclusions demonstrating a Maltese cross appearance under polarized light.^{36,37} This corresponds to radially-oriented amyloid fibrils that are seen within phagosomes of macrophages on electron microscopy (figure 3). Macrophage phagocytosis of amyloid³⁸⁻⁴⁰ and spherulites composed of radially oriented accumulation of amyloid fibrils^{36,41} have been infrequently described previously. The prominence of this unusual finding in our case might relate to the composition of amyloid fibrils with the ApoA1 wild type protein, possibly allowing for this vigorous, albeit futile, effort to clear the amyloid through normal targeting mechanisms. Furthermore, the biopsy seems to have captured a histologic snapshot of an active, vigorous process of phagocytosis and therefore likely contains both preprocessed and proteolyzed ApoA1. This may explain the presence of sequences both within and outside of the 93-residue amino terminal segment of ApoA1 previously reported to be amyloidogenic in all instances of both mutant and wild type ApoA1 amyloidosis. It is notable in our case that the perineurium, known to be a site of macrophage activation and senescence, is seen to be prominently involved by both amyloid deposits and inflammatory infiltrates. This lends further support to the hypothesis in this case that inflammation acted locally in combination with other amyloidogenic features to allow for the dramatic focal ApoA1 amyloidosis.

For clinicians, a consideration of amyloidoma in the differential diagnosis is problematic, especially in the absence of circulating monoclonal proteins, as was the case in our patient. Imaging led to consideration of a potentially treatable form of regional hypertrophic inflammatory neuropathy, and a prudent but unsuccessful immune treatment trial. Targeted biopsy combined with laser dissected mass spectrometric-analysis provided for the diagnosis. In our patient, orthopedic bracing and continued monitoring for development of a monoclonal gammopathy is planned. Currently there are no proven treatments for neural amyloidomas, including those with circulating monoclonal proteins.⁴² Hopefully, emerging new strategies to reduce associated amyloid proteins and hence the amyloid fibrils,⁴³ and therapeutics to change energy kinetics away from the fibril forming constitutives⁴⁴ may ultimately help such patients. Considering the reported proamyloidogenic effects on ApoA1 of local inflammatory processes such as atherosclerosis, future trends in treatment of similar patients might continue toward anti-inflammatory as well as statin and anti-oxidant medications.

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Abbreviations

ApoA1	Apolipoprotein A1
TTR	transthyretin
DNA	deoxyribonucleic acid
MR	magnetic resonance
Gly26Arg	glycine 26 arginine
Leu178His	leucine 178 histidine
WT	wild type
PMP-22	peripheral myelin protein 22
ANCA	anti neutrophil cytoplasmic antibody
RF	rheumatoid factor
CCP	cyclic citrullinated peptide
TSH	thyroid stimulating hormone
ACE	angiotensin converting enzyme
PET/CT	Positron Emission Tomography/Computed Tomography
FDG	Fludeoxyglucose
EMA	epithelial membrane antigen
CD	cluster of differentiation
SAP	serum amyloid P component
SAA	serum amyloid A protein
SNAP	sensory nerve action potential
CMAP	compound muscle action potential
MUP	motor unit potential
IgG	immunoglobulin G
LMD-MS	laser microdissection mass spectroscopy
HDL	high density lipoprotein
LCAT	lecithin cholesterol acyltransferase

Figure 1.

3 Tesla MRI of the pelvis demonstrated marked enlargement and T2 hyperintensity of the right L4-S3 nerve roots (arrows), extending along the lumbosacral plexus to the level of the sciatic notch on axial (A) and coronal (B) images. Denervation edema and atrophy were seen in the right gluteus maximus (arrow head).

Figure 2.

Osmiflicated teased fiber preparation (A) showed mostly empty fibers, often with adherent, amorphous, flocculent material. On methylene blue-stained epoxy-embedded semithin sections (B), a severely decreased density of myelinated fibers is seen, with only rare, intermediate sized fibers seen (arrow head), and frequent spherical aggregates of amorphous material (arrows). Congo red stained sections (C) revealed the endoneurium (asterisk) and perineurium (arrow) of some fascicles to be completely effaced by congophilic, amorphous material which was diffusely birefringent under polarized light (D), diagnostic of amyloidosis. A large, subperineurial collection of inflammatory cells was seen in one fascicle (arrow head – panel C) displacing surrounding amyloid.

Figure 3. The biopsied material showed frequent round intracellular inclusions scattered throughout the endoneurium which were congophilic (B) and displayed Maltese crosses with polarized light (A). Electron microscopy revealed starburst-shaped inclusions within mononuclear cells (C) demonstrated to be macrophages in conjunction with immunohistochemical preparations. At higher magnification (D) criss-crossing fibril formations typical of amyloid are seen.

M K A A V L T L A Y	L F L T G S Q A R H	F W Q Q D E P P Q S	P W D R Y K D L A T	Y Y Y D Y L K D S G
R D Y V S Q F E G S	A L G K Q L N I K L	L D N W D S V T S T	F S K L R E Q L G P	V T Q E F W D N I F
K E T E G L R Q E M	S K D L E E V K A K	V Q P Y L D D F Q K	K W Q E E M E L Y R	Q K V E P L R A E L
Q E G A R Q K L H E	L Q E K L S P L G E	E M R D R A R A H V	D A L R T H L A P Y	S D E L R Q R L A A
R L E A L K E N G G	A R L A E Y H A K A	T E H L S T L S E K	A K P A L E D L R Q	G L L P V L E S F K
V S F L S A L E E Y	T K K L N T Q			

Figure 4. ApoA1 Sequence and Identified Amino Acid Digests

Mass spectrophotometry identified sequences throughout the ApoA1 protein, representing 113 of 267 of the total amino acids (i.e. 42% of the total protein, identified and highlight yellow). One oxidated methionine residue was identified (highlighted green). The identified sequences were both within and outside the 93 amino acid amino terminal segment previously identified as amyloidogenic.