



Case Report

Unraveling a rare cause of spinal stenosis: Coexistent AL and ATTR amyloidosis involving the ligamentum flavum

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ABSTRACT

Background: Amyloidosis is a protein misfolding disorder that leads to the deposition of beta-pleated sheets of a fibrillar derivative of various protein precursors. Identification of the type of precursor protein is integral in treatment decision-making. The presence of two different types of amyloid in the same patient is unusually rare, and there are no previous reports of two different types of amyloid deposition in the ligamentum flavum (LF) in the same patient.

Case Description: Here, we describe two patients with spinal stenosis who underwent laminectomies and were found to have AL and ATTR amyloid deposits in the LF.

Conclusion: As the spine is becoming recognized as a site for ATTRwt amyloid deposition, patients undergoing spinal decompression surgery may potentially benefit from evaluation for amyloidosis in the LF.

Keywords: Ligamentum flavum, Light chain, Spinal stenosis, Wild-type transthyretin amyloid

INTRODUCTION

Systemic light chain (AL) amyloidosis is one of the most common types of amyloidosis, although over 30 other proteins are implicated in this rare disease.^[3,21] Patients with AL amyloidosis usually have multiorgan involvement, predominantly in the heart and the kidneys, but can also have musculoskeletal involvement.^[17] Once amyloid deposition is noted by Congo red or electron microscopy, identification of the precursor protein is paramount for prognostic and treatment considerations. Amyloidosis due to the buildup of wild-type transthyretin protein (ATTRwt), in addition to being a cause of heart failure in older adults, is also increasingly being found in the ligaments and tendons, especially in association with carpal tunnel syndrome and spinal stenosis.^[1,10,11,19] The presence of two different types of amyloid in the same tissue is very rare and there are no prior reports of dual amyloid deposits in the ligamentum flavum (LF).^[4,6,12,13,16,18] Here, we describe two patients with spinal stenosis who each had coexistent AL and ATTR amyloid deposits in the LF.

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CASE DESCRIPTION

Patient 1

A 69-year-old man with 4 years of smoldering IgG lambda myeloma was seen for concern of systemic light-chain amyloidosis due to macroglossia, worsening fatigue, and unintentional weight loss. He had a prior history of C3-T1 cervical laminectomy and decompression with fusion 2 years prior. An abdominal fat pad aspirate showed focal congophilia and faint birefringence under polarized

light. Bone marrow biopsy showed involvement with 30–40% plasma cells and amyloid deposits by Congo red staining. Over the prior year, he had developed progressive lower back pain and required the use of a wheelchair. Magnetic resonance imaging (MRI) of the spine showed severe spinal stenosis at L4-L5. He underwent posterior L4-L5 laminectomies, medial facetectomies, and decompression of the thecal sac [Figure 1a]. The excised LF was 2.5 × 1.5 × 0.4 cm in dimension and pathologic examination showed soft-tissue clonal plasma cell

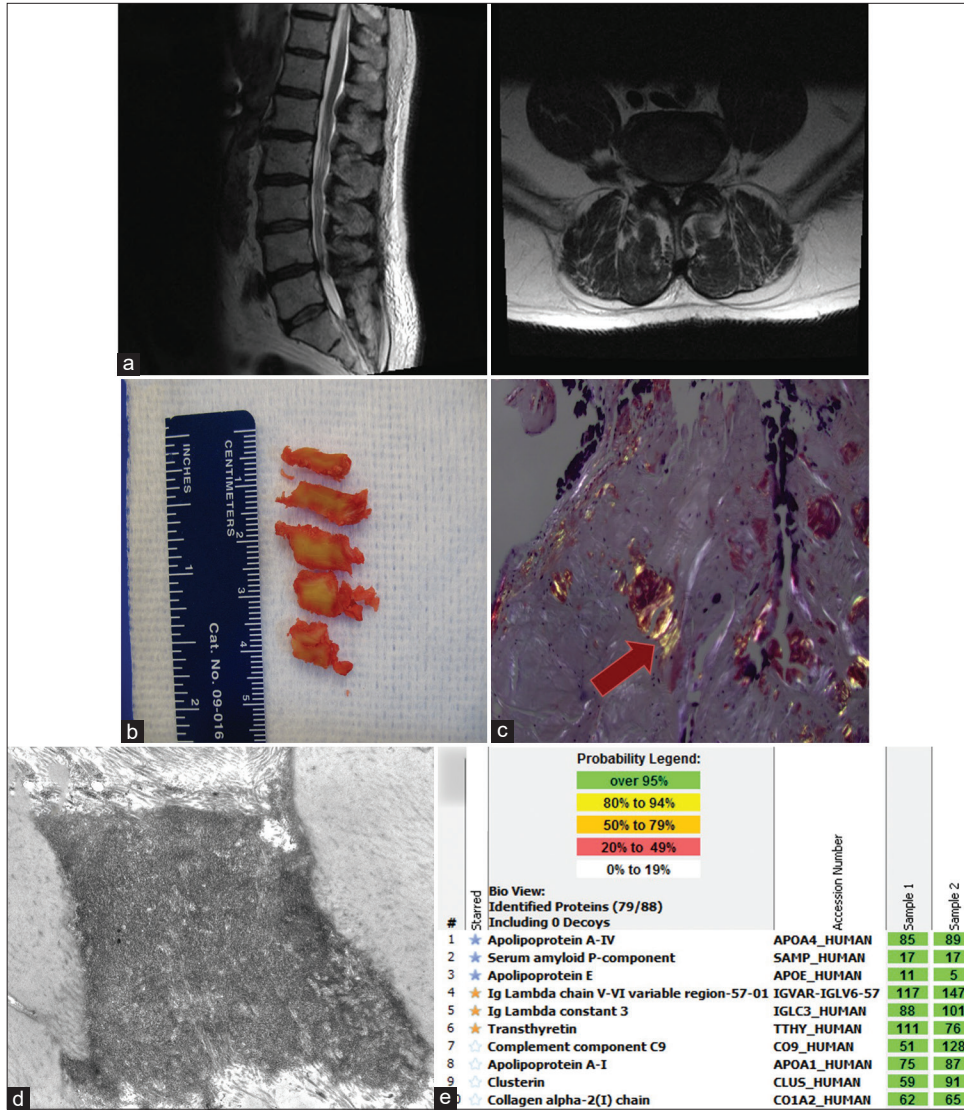


Figure 1: Imaging and pathology for Patient 1. (a) T2-weighted preoperative magnetic resonance imaging; left: sagittal view, right: axial view at the L4-L5 level showing thickened ligamentum flavum. (b) Gross ligamentum flavum specimens resected from surgery. (c) Congo red stains under polarized light, showing apple green birefringence (indicated by arrow). (d) Electron microscopy of ligamentum flavum showing amyloid deposit. (e) Liquid chromatography tandem mass spectrometry (LC-MS/MS) performed on peptides extracted from Congo red-positive microdissected areas of paraffin-embedded specimen, peptide profile consistent with ATTR (transthyretin)-type amyloid and AL (lambda)-type amyloid. Yellow stars indicate the amyloid precursor proteins (transthyretin and lambda light chains) and blue stars indicate the universal amyloid proteins (apolipoprotein A-IV, serum amyloid P-component, and apolipoprotein E). The total number of MS/MS spectra matching to a protein in a sample is shown in the green boxes. Two independent samples were analyzed per case.

infiltration (8%) with amyloid by Congo red staining in the soft tissue and vessels [Figures 1b, c, and d]. LC/MS confirmed both ATTR- and AL (lambda)-type amyloid deposits [Figure 1e]. A TTR amino acid abnormality indicative of a TTR gene mutation was not identified by LC-MS/MS. At the time of his surgery, serum lambda light-chain level was 623 mg/L. He then began anti-plasma cell therapy with daratumumab and dexamethasone.

Patient 2

A 76-year-old male with a known diagnosis of IgG kappa multiple myeloma with skeletal involvement for the past 8 years had been previously treated with RVD (lenalidomide, bortezomib, and dexamethasone) and Id (ixazomib and dexamethasone). Nine months before his surgery, he had disease progression with new bone lesions, for which he was started on pomalidomide and dexamethasone. At that time, he was also found to have atrial fibrillation and new-

onset systolic heart failure with an ejection fraction of 45% on echocardiogram. He was evaluated for worsening lower back pain and MRI showed loss of height at T10 and mild retropulsion of the posterior aspect of the T6 and T10 vertebral bodies causing neuroforaminal stenosis at T10-T11 and T11-T12 [Figure 2a].

He underwent an uneventful decompressive T10-T11 laminectomy; the excised LF was a 3 × 1.5 × 0.5 cm aggregate of pink-red fibrous rubbery tissue. Congo red stain showed multifocal congophilic deposits that had apple green birefringence under polarized light [Figure 2b]. Liquid chromatography tandem mass spectrometry (LC-MS/MS, Mayo Clinic Laboratories, Rochester, MN, USA) was used for typing and detected a peptide profile consistent with ATTR (transthyretin)-type and kappa light chain-type amyloid deposition [Figure 2c]. A TTR amino acid abnormality indicative of a TTR gene mutation was not identified by LC-MS/MS. These findings confirmed

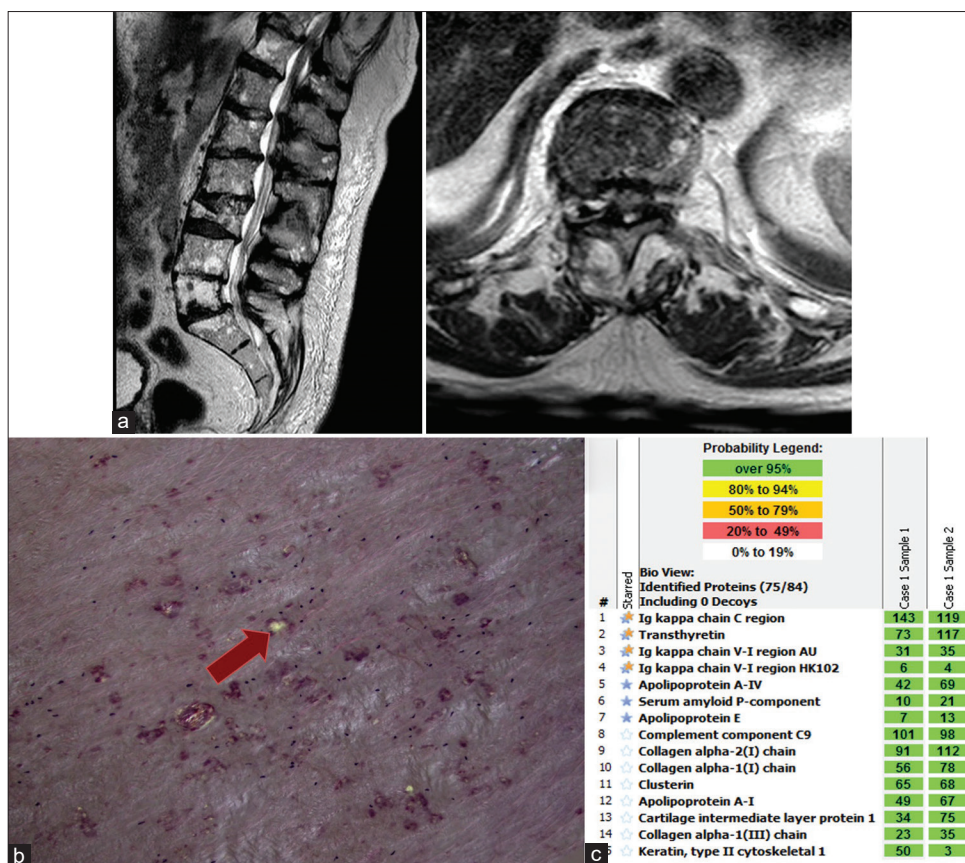


Figure 2: Imaging and pathology for Patient 2. (a) T2-weighted preoperative magnetic resonance imaging; left: sagittal view, right: axial view at T10-T11 level showing thickened ligamentous flavum. (b) Congo red stains under polarized light, showing apple green birefringence (indicated by arrow). (c) Liquid chromatography tandem mass spectrometry (LC-MS/MS) performed on peptides extracted from Congo red-positive microdissected areas of paraffin-embedded specimen detected a peptide profile consistent with ATTR (transthyretin)-type amyloid and AL (kappa)-type amyloid. Blue/yellow stars indicate the amyloid precursor proteins (transthyretin and kappa light chains) and blue stars indicate the universal amyloid proteins (apolipoprotein A-IV, serum amyloid P-component, and apolipoprotein E). The total number of MS/MS spectra matching to a protein in a sample is shown in the green boxes. Two independent samples were analyzed per case.

that the amyloid precursor proteins were transthyretin and kappa light chains. Before his surgery, he had a serum IgG kappa monoclonal protein level of 1.28 g/dL, serum kappa-free light-chain level of 90.3 mg/L, and a serum FLC ratio of 17.7.

DISCUSSION

The two patients described above presented with spinal stenosis and surgically resected LF showed amyloid deposits that were derived from both circulating free light chains and transthyretin protein. Both patients had symptoms of rapidly progressive myelopathy, which suggests that the AL amyloid deposited simultaneously in the spine as other tissues and was a contributing cause to spinal stenosis. These findings present a unique problem for a rare disorder as more than 1 type of amyloidosis in the same patient is rarely encountered.

Spinal stenosis is a progressive degenerative condition that results in significant morbidity and disability affecting up to 20% of persons above the age of 60.^[7,9] LF hypertrophy is an important pathological process contributing to this debilitating condition.^[2,22] Organ tropism in amyloidosis may correspond to the amyloid type, and in case of light-chain amyloidosis, also by the light-chain variable region genes.^[5] Identification of the precursor protein by mass spectrometry is a gold standard for diagnosis and can identify the protein constituents of the amyloid deposits.^[20] Recent studies have indicated that ATTRwt deposition in the spine is common in patients with spinal stenosis and prevalence of concurrent cardiac involvement is rare.^[8]

Our two cases raise the question of whether the presence of ATTR amyloid in the LF provides a nidus for seeding and propagation for other types of amyloid fibrils. The significance of these findings requires careful contemplation as the presence of ATTR amyloid in the spinal ligament might represent a localized form of amyloidosis which may precede the development of cardiac amyloidosis as is the case with carpal tunnel syndrome.^[19] Treatment with TTR tetramer stabilizers or silencers is not currently indicated for those without cardiac amyloidosis or amyloid polyneuropathy. The question arises; however, if patients with ATTRwt causing spinal stenosis will develop cardiac amyloidosis later in life. Moreover, it is unclear whether ATTR in the LF provides seeding for the propagation for other types of amyloid fibrils.

Review of literature for previously reported cases of two different types of amyloidosis in the same patient is provided in [Table 1]. Among these patients who had both ATTR and AL amyloidosis, heart and bone marrow were the usual sites but none of these reported patients had the spine as a site for two different types of amyloid.

As survival improves for patients with AL amyloidosis, it is possible that some of them would also develop ATTRwt amyloidosis later in life.^[15] ATTRwt cardiac amyloidosis can contribute to further morbidity and may also lead to additional chemotherapy. Although noninvasive diagnosis of ATTR cardiac amyloidosis is broadly useful to identify such patients, endomyocardial biopsy is likely needed in such cases to confirm the type of amyloid present since treatment varies accordingly.^[14]

Table 1: Previous case reports of patients with dual amyloid deposition.

| Study | Age | Gender | Presenting SYMPTOMS | Amyloid types | Confirmed sites |
|--------------------------------|-----|--------|---------------------------------------|------------------------|-----------------------------------|
| Papa <i>et al.</i> , 2019 | 31 | F | Dysuria and hematuria | AA and AL (lambda) | Kidneys |
| Sidiqi <i>et al.</i> , 2019 | 86 | F | Gastrointestinal | ATTR and SAA | Stomach and fat |
| | 74 | M | Cardiovascular | ATTR and AIns | Heart and fat |
| | 84 | M | Proteinuria | AL (lambda) and ATTR | Kidney and bone marrow |
| | 90 | M | Postmortem | ATTR and A-IA | Heart and duodenum |
| | 59 | M | Proteinuria | AL (lambda) and ATTR | Bone marrow (both) and fat |
| | 59 | M | Lymphadenopathy | AL (kappa) and ATTR | Bone marrow (both) and lymph node |
| | 79 | M | Cardiovascular | AL (lambda) and ATTR | Heart (both) and Kidney |
| | 70 | M | Myopathy | AL (kappa) and ATTRm | Bone marrow |
| | 66 | M | Cardiovascular | AL (lambda) and ATTR | fat and heart (both) |
| de Sousa <i>et al.</i> , 2000 | 41 | F | Dysphonia | ApoAI and ATTR | Larynx (both) and skin (both) |
| Bergstrom <i>et al.</i> , 2004 | 92 | M | Heart failure | ApoA-IV and ATTR | Heart |
| Mahmood <i>et al.</i> , 2014 | 81 | M | Heart failure | AL (lambda) and ATTR | Heart |
| Martini <i>et al.</i> , 2019 | 73 | M | Kidney | SAA and ATTRwt | Fat pad |
| | 70 | M | Renal, cardiac | AL (lambda) and ATTRwt | Heart and fat pad |
| | 76 | M | Renal | AL (kappa) and SAA | Fat pad |
| | 80 | M | Renal, peripheral neuropathy, cardiac | AL (lambda) and ATTRwt | Fat pad |

CONCLUSION

As the spine is increasingly being recognized as a site for ATTRwt amyloid deposition, patients with plasma cell disorders undergoing surgery for spinal stenosis may potentially benefit from evaluation for amyloidosis in the LF. If amyloid deposits are noted, identification of the type of amyloidosis is important as several different types of amyloid can occur simultaneously in the same tissue. Recognizing the types of amyloid provides the opportunity to screen for the involvement of other body sites with subsequent therapeutic implications.

Declaration of patient consent

Patient consent not required as patient identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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