

Fatal TTR amyloidosis with neuropathy from domino liver p.Val71Ala transplant

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Neurol Genet 2019;5:e351. doi:10.1212/NXG.0000000000000351

Familial transthyretin (TTR) amyloidosis (FTA) is a serious autosomal dominant neuropathy caused by TTR germline mutations that lead to death on average 10 years from symptom onset. The mutant tetramer protein is produced predominantly in the liver, and liver transplantation is commonly performed to reduce the production of the mutant protein.¹ The otherwise well-working explanted TTR liver can be transplanted into recipients who require liver transplantation but are unable to receive a liver in a timely fashion, the so-called domino liver transplant (DLTX). Recently, oligonucleotide drugs that reduce circulating TTR have been approved by the Food and Drug Administration (FDA), and these drugs use either antisense (inotersen) or RNA interference (patisiran), whereas earlier tetramer-stabilizing drugs (tafamidis and diflunisal) were less efficacious.² Herein, we describe a domino liver recipient who died of respiratory failure from transplanted p.Val71Ala amyloidosis.

Case report

A 70-year-old man with nonalcoholic steatohepatitis cirrhosis underwent DLTX from a 40-year-old man with TTR p.Val71Ala amyloidosis and neuropathy. The recipient was otherwise healthy and had no personal or family history of neuropathy (10 brothers and sisters). He initially did well, but 3 years after transplant developed pain in the feet with symmetric sensory loss and ankle weakness. He was treated with IV immunoglobulin and pulse steroids, but progressed with weight loss (40 lbs), orthostasis, and postprandial diarrhea. His liver continued to function well on tacrolimus and oral prednisone.

He was referred 2 years from neuropathy onset unsafe to walk, having proximal and distal extremity weakness (Medical Research Council strength: 1/5 bilaterally below knees and elbows; 2/5 bilaterally at the thighs and shoulders). He was hyporeflexic and had dense sensory loss for heat pain and proprioception extending to the shins. Nerve conductions were abnormal, compound muscle action potential (peroneal 0.2, normal > 2.0 mV; tibial 0.3, normal > 4.0 mV; ulnar 3.2 mV, normal > 6.0 mV) and sensory nerve action potential (sural 0.0, normal > 0.0 uV; median 0.0, normal > 15 uV; ulnar 2.0, normal uV > 10.0 uv) without demyelination. Needle EMG showed neurogenic potentials with fibrillations extending to the arms and thighs, all consistent with a severe axonal sensorimotor polyneuropathy. Autonomic testing showed patchy postganglionic sudomotor abnormality by quantitative sudomotor autonomic reflex testing and moderate adrenergic and severe cardiovagal impairment by tilt table evaluation with Valsalva maneuver. Echocardiogram was normal 13 months before death, but ^{99m}Tc-hydroxyethylene diphosphonate single-photon emission computed tomography and needle EMG or nerve conductions of the diaphragm were not performed. Urine analysis revealed proteinuria 454 mg (normal <167 mg/24 hours), with creatinine clearance

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Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the Mayo Clinic.

Ethical statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Approval for this study was obtained by the Institutional Review Board at the Mayo Clinic, and the patient provided written consent to participate.

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68 mL/min (normal 77–130 mL/min/body surface area). Multiple tests were unremarkable: serum immunofixation, CSF PCR (cytomegalovirus, Epstein-Barr virus, and burgdorferi), serum thyroid stimulating hormone, B12, folate, copper, C-reactive protein, MRI of the spine, CT of the chest-abdomen-pelvis, and bone marrow flow cytometry for lymphoma.

Sural nerve and bone marrow biopsies showed infiltration by amyloid with occasional inflammatory cells seen in the nerve (figure). TTR DNA sequencing from his blood was negative for mutation. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) performed on the amyloid infiltration from the bone marrow and nerve specimens confirmed TTR p.Val71Ala amyloidosis in both specimens (figure). Repeat liver transplant was considered, but he was not a candidate based on the severity of neuropathy and his age. He was unable to tolerate diflunisal due to gastrointestinal upset. He died 5 years and 1 month from the time of transplantation with respiratory failure.

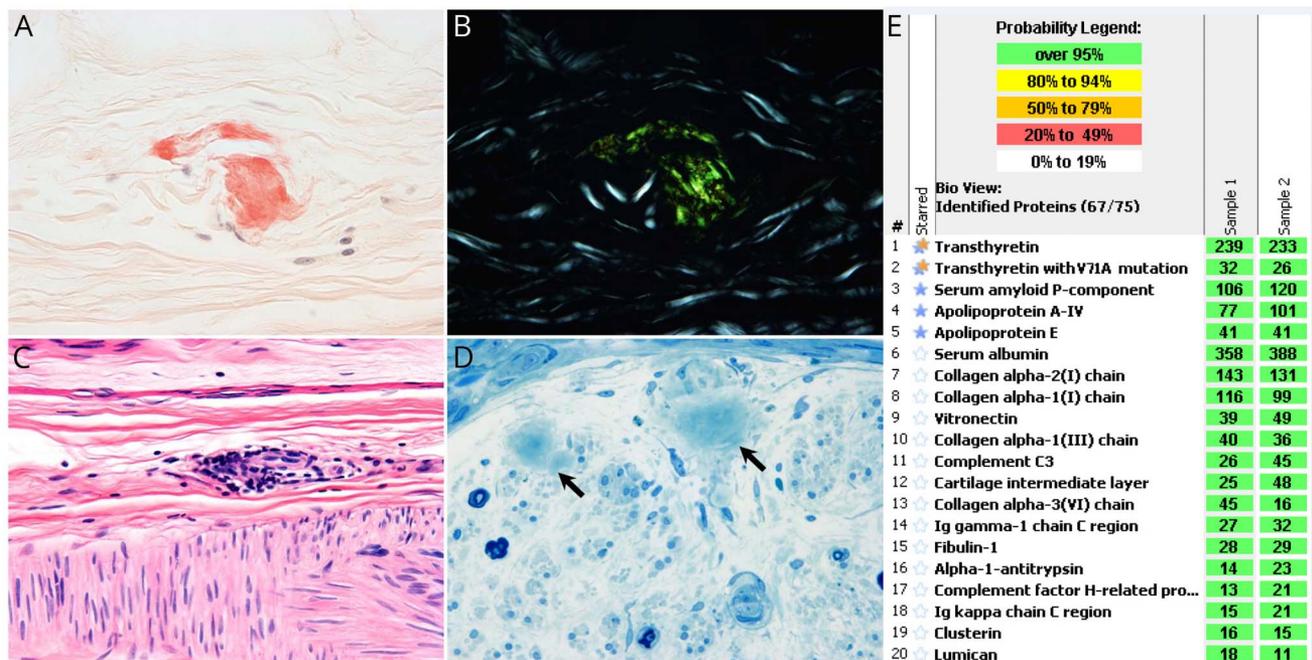
Discussion

Amyloid transthyretin p.Val71Ala amyloidosis has been associated with young onset of disease (in the 30s and 40s), as occurred in the living donor of our patient.³ Recent 20-year review of the familial amyloid polyneuropathy World

Transplant Registry identifies 11 TTR p.Val71Ala persons having undergone liver transplant.¹ One p.Val71Ala DLTX recipient aged 59 years developed neuropathy and cardiomyopathy 5 years after transplant but was still alive 9 years later.⁴ Our patient was considerably older (70 years) at the time of transplant, and older age has been identified as an important accelerator of domino recipient amyloid neuropathy.⁵ The limited inflammation in our case seems coincidental occurring in up to one-third of amyloid sural nerve biopsies.⁶ The problems experienced by domino recipients related to mutant TTR are increasingly recognized. Prospective investigations of neuropathy within domino recipients have identified common (one-fourth affected) pathologic nerve amyloid infiltration with symptomatic neuropathy.⁷ Although patients were reported to have symptoms mimic FTA, our patient seems to have worse severity.

Neurologic improvements in FTA can occur not only in those receiving early-onset liver transplantation¹ but also those treated early with the new FDA-approved drugs.² A theoretical advantage of the new oligonucleotide therapies is that they reduce both wild-type and mutant TTR, both linked to disease progression. However, before consideration of these drugs in DLTX-affected patients, mutant TTR will likely need to be confirmed by LC MS/MS, as diagnosis of mutant TTR by blood DNA will not be possible.

Figure Nerve biopsy and proteomic analysis of ATTR p.Val71Ala domino liver amyloidosis



(A) Congo red–stained characteristic microvessel in nerve (B) confirmed to be amyloid under fluorescent birefringence. (C) Epineurial microvessel with small inflammatory cell collections of unclear significance. (D) Semithin epoxy sections with acellular lardaceous accumulations characteristic of amyloid deposition and marked nerve fiber reductions. (E) ATTR p.Val71Ala was identified proteomically in both nerve and bone marrow (bone marrow data shown). Congo red–positive amyloid was microdissected and analyzed using liquid chromatography–tandem mass spectrometry (LC-MS/MS) (chymotrypsin modification). The protein identification report shows the type-specific markers (ATTR and ATTR with Val71Ala mutation, highlighted with blue/gold stars) and the universal amyloid markers (highlighted with blue stars). The total number of MS/MS spectra matched to the listed protein is represented by the numbers displayed in green boxes. Two independent microdissections with subsequent LC MS/MS analysis are shown. The arrows indicate acellular homogenous collections typical of amyloid. ATTR = amyloid transthyretin.

Study funding

This work was supported by the Mayo Clinic Foundation and the Department of Laboratory Medicine and Pathology, Rochester, MN.

Disclosure

Disclosures available: [Neurology.org/NG](https://www.neurology.org/NG).

Publication history

Received by *Neurology: Genetics* April 26, 2019. Accepted in final form July 1, 2019.

Appendix Authors

Name	Location	Role	Contribution
Ross Puffer, MD	Mayo Clinic, Rochester, MN	Author	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Robert J. Spinner, MD	Mayo Clinic, Rochester, MN	Author	Interpreted the data and revised the manuscript for intellectual content
Sharma Rishi	Mayo Clinic, Rochester, MN	Author	Interpreted the data and revised the manuscript for intellectual content
Yucai Wang, MD	Mayo Clinic, Rochester, MN	Author	Interpreted the data and revised the manuscript for intellectual content
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Appendix (continued)

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Christopher J. Klein, MD	Mayo Clinic, Rochester, MN	Author	Designed and conceptualized the study; analyzed the data; and revised the manuscript for intellectual content

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DOI 10.1212/NXG.0000000000000351

This information is current as of August 14, 2019

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