Oxford Medical Case Reports, 2021, **11**,443–446
https://doi.org/10.1093/omcr/omab113
Case Report

Can lightning strike twice? Wild-type transthyretin cardiac amyloidosis associated with rare liver disease

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Abstract

Wild-type ATTR cardiac amyloidosis (ATTRwt-CA) is not as rare as previously thought to be. Patients with infiltrative cardiac amyloidosis often present with right-sided heart failure (HF) symptomatology. Clinically significant liver disease and cirrhosis has not been reported in ATTRwt-CA. We present two cases of ATTRwt-CA with right-sided HF and abnormal liver function tests initially thought to be secondary to congestive hepatopathy but found to have rare and unrelated liver disease. These cases highlight the importance of developing a broad differential diagnosis and leveraging a multidisciplinary team approach in evaluating patients for unusual causes of cirrhosis/other chronic liver diseases when ATTR cardiac amyloidosis patients present with congestive hepatopathy.

INTRODUCTION

Wild-type ATTR cardiac amyloidosis (ATTRwt-CA) has an age-dependent penetrance and is typically diagnosed in males above 60 years of age. Previous autopsy studies demonstrate that 25% of octogenarians have myocardial deposits of amyloid composed of transthyretin [1]. In a study of 109 patients with ante-mortem diagnosis of heart failure with preserved ejection fraction (HFpEF), 17% had ATTRwt-CA myocardial deposits with 5% having moderate to severe interstitial deposition indicative of a causative etiology of HFpEF [2].

In ATTRwt-CA, the circulating TTR tetramer, synthesized in the liver, destabilizes and subsequently aggregated TTR form amyloid fibrils that deposits in the myocardium causing heart failure (HF) and arrhythmias [1]. Symptoms of right-sided HF are common including elevated central venous pressures, hepatomegaly and edema [3]. Clinically significant liver disease and cirrhosis is not commonly reported in ATTRwt-CA.

CASE REPORTS

Case 1

A 77-year-old male with history of atrial fibrillation (AF) resistant to direct current cardioversion (DCCV) and dofetilide therapy with post-procedural cerebrovascular accident and subsequent radiofrequency ablation (RFA) and watchman placement presented with symptoms of HF. Workup (Table 1) suggested an infiltrative cardiomyopathy and ATTRwt-CA was diagnosed by a non-biopsy approach with a positive Tc-PYP scan (Fig. 1A-B) and the absence of monoclonal proteins on serologic testing [3]. He was managed with a bioavailable loop-diuretic and tafamidis. Over next 2 years, he was noted to have abnormal liver function tests (LFTs) (ALP = 165 U/L and GGT = 1185 U/L). Abdominal ultrasound showed hepatosplenomegaly with pulsatile main portal vein waveforms suggestive of right heart dysfunction in the setting of moderate-to-severe tricuspid regurgitation along with small amount of ascites. A computerized tomography of the abdomen and pelvis (CTAP) showed moderate abdominal ascites, without abnormal liver findings or splenomegaly.

Initially this was attributed to passive hepatic congestion. However, liver biopsy was performed due to the worsening LFTs (ALP 566 U/L and GGT 1424 U/L) that revealed hepatic venous outflow obstruction from his HF as well as features of alpha-1 antitrypsin deficiency (A1AT-D) (Fig. 2A-B). There was no cirrhosis, or portal hypertension by pressure measurement. The A1AT level was 101 mg/dl (reference level: 100–190 mg/dl) and genotyping confirmed an MZ phenotype. He was referred to experts in A1AT-D and underwent a chest CT showing no emphysema. Pulmonary function tests showed an FEV1 of 2.3 L (71%), FVC of 3.3 L (73%), FEV1/FVC (70%),

Received: July 9, 2021. **Revised:** August 17, 2021. **Accepted:** October 14, 2021

Table 1. Patient characteristics

	Case 1	Case 2
ATTRwt-CA diagnosis	Tc99m PYP study semiquantitative score of 3 and quantitative H/CL ratio of 1.93 indicative of ATTR in the absence of monoclonal proteins	EMB with multiple small amorphous infiltrates positive with Congo Red stain and apple green birefringence under polarized light. Liquid Chromatography tandem Mass Spectrometry with ATTR subtype, no iron stores
Electrocardiogram	Sinus bradycardia, left axis deviation with first-degree atrioventricular block, low limb voltage with QRS duration 108 ms, incomplete right bundle branch block.	Normal sinus rhythm, first-degree atrioventricular block (PR 296 ms), low limb voltage with QRS duration 104 ms and poor precordial R wave progression.
Initial TTE	Intraventricular-septal thickness 17 mm, posterior wall thickness of 12 mm, LVEF 60%, mild-to-moderate tricuspid regurgitation, RVSP of 35–40 mmHg.	LV mass index of 134 grams/m2, restrictive mitral inflow, LVEF of 60%, LA volume index of 32 ml/m2, IVS of 16 mm, PWT of 16 mm
Cardiac MRI	Apparent diffuse wall thickening of left ventricle with patchy myocardial enhancement on delayed postcontrast imaging	Normal LV size with severe concentric wall thickening and normal systolic function. Normal RV size and systolic function. Diffuse myocardial enhancement predominantly involving the intramyocardial to subendocardial regions and abnormal contrast kinetics between blood and myocardium.
Other abnormal testing	Elevated LFTs predominantly ALP 165 U/L increased to 566 U/L and GGT 1185 U/L increased to 1424 U/L, AFP 2.6 ng/ml (within normal range), A1AT level 101 mg/dl	Transferrin saturation 75%, ferritin 543 ng/ml, ALP 640 U/L that normalized post-transplant
Genetic testing	-No TTR mutation detected -A1AT MZ carrier status	-No TTR mutation detected -HFE C282Y Homozygous mutation
Liver Biopsy findings	-Mild cardiac sclerosis consistent with congestive heart failure -No iron deposits -Periportal zones with increased intrahepatic PASD positive globules positive for A1AT-D	-Bridging fibrosis in setting of cardiac sclerosis -Marked hemosiderosis—Congo red stain negative
Treatment	Vyndamax (tafamidis)	Combined OHT and OLT with HCV donor, treated with Mavyret (glecaprevir/pibrentasvir), remains SVR
Long-term outcome during 3-year follow-up visits	Alive, maintained on dopamine infusion, diuretics and Vyndamax (tafamidis)	Alive, on dual immunosuppression with Prograf (tacrolimus) and Cellcept (mycophenolate mofetil). No transplant rejection, last EF preserved, last RHC with good hemodynamics and no CAV on LHC

A1AT-D: alpha-1 antitrypsin deficiency, CAV: cardiac allograft vasculopathy, EMB: Endomyocardial biopsy, GGT: Gamma glutamyl transferase, HCV: Hepatitis C Virus, OHT: Orthotopic heart transplant, OLT: Orthotopic Liver Transplant, PASD: periodic acid Schiff diastase stain, SVR: sustained virological response

TLC of 9.1 L (128%) with a DLCO 79%. He was advised to obtain annual Pulmonary function tests (PFTs) and genetic testing of first-degree relatives for A1AT-D was recommended.

Case 2

A 64-year-old male with a past medical history of HFpEF (NYHA class IIIB) status-post placement of an automated implantable cardioverter defibrillator, AF status-post RFA and several DCCVs on dabigatran presented with worsening HF symptoms. He was diagnosed with ATTRwt-CA (Table 1) via endomyocardial biopsy (Fig. 1C–E). Over the next 3 years he had worsening symptoms of right HF and worsening central hemodynamics: RA pressures 16 mm Hg, PA pressures 63/33 (mean-PAP of 45 mm Hg), PCWP 22 mm Hg with CO 5.15 L/min and CI 2.6 L/min/m2, PVR 4.47 WU. During his heart transplant evaluation, a CTAP revealed concern for cirrhosis with stigmata of portal hypertension, including large gastric and esophageal varices. Hepatology recommended transjugular liver biopsy, which was negative for portal hypertension by pressure measurement. Pathology revealed features of cardiac sclerosis with bridging fibrosis. There were no fully developed nodules, thus no established cirrhosis. Unexpectedly, there was no evidence of amyloid deposit with Congo red stain negative, but routine iron staining showed grade 4 of 4 hepatocyte iron, without significant Kupffer cell iron, suggesting hemochromatosis (Fig. 3A–C). Hematologic evaluation revealed a transferrin saturation of 71%, ferritin 543 ng/ml and on HFE genetic testing he was a C282Y homozygote. He received biweekly phlebotomies and eventually underwent combined heart and liver transplant with an HCV-positive donor (genotype 1a). Post-transplant, patient completed 12-week course of glecaprevir–pibrentasvir and achieved a sustained virologic response. During follow-up over 3 years, patient has had no episodes of acute rejection with preserved graft function and no cardiac allograft vasculopathy. LFTs and iron studies have been within normal range with no significant symptoms. Patient is currently maintained on dual immunosuppression therapy with tacrolimus and mycophenolate-mofetil.

DISCUSSION

The recognition of ATTRwt-CA has changed over the last decade, with wider availability of Tc-PYP scanning for noninvasive diagnosis and availability of novel therapies that stabilize the transthyretin molecule. Although

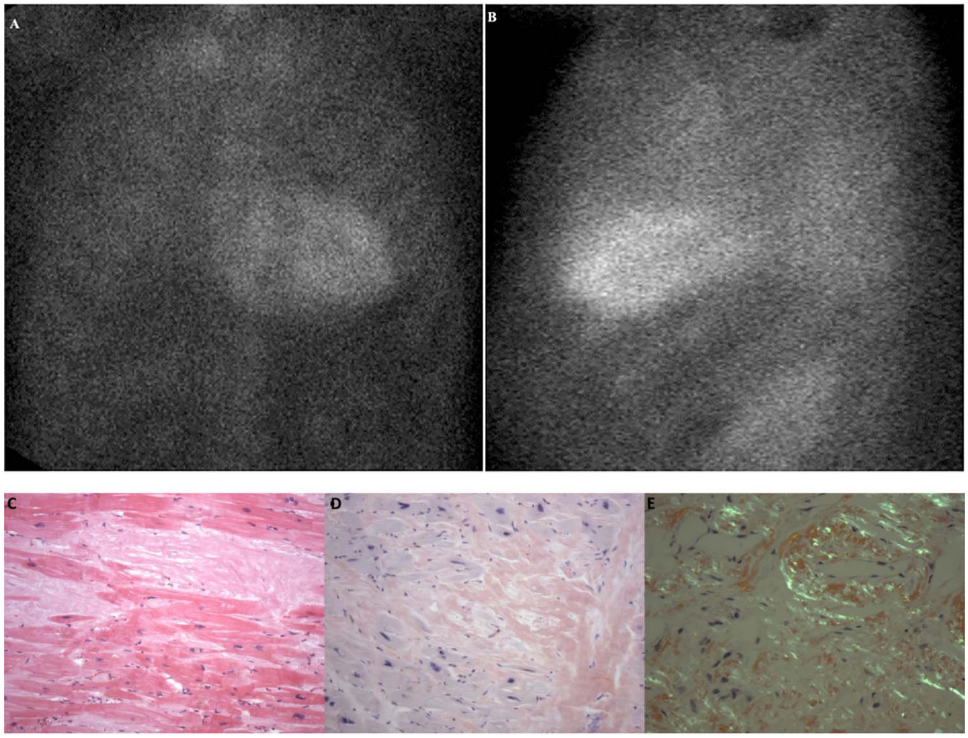

Figure 1. Cardiac amyloid findings on Tc-PYP amyloid scan and endomyocardial biopsy. A: Technetium pyrophosphate (Tc-PYP) scan showing diffuse myocardial uptake on planar imaging via antero-posterior view. B: Tc-PYP lateral view. C: H&E with extensive pink amorphous patchy and diffuse interstitial deposits of amyloid with no involvement of intramyocardial vessels. D: Amyloid infiltration of the myocardium (Congo red stain, 100x); E: Amyloid deposits demonstrating apple green birefringence on polarized microscopy following Congo red staining, 100x.

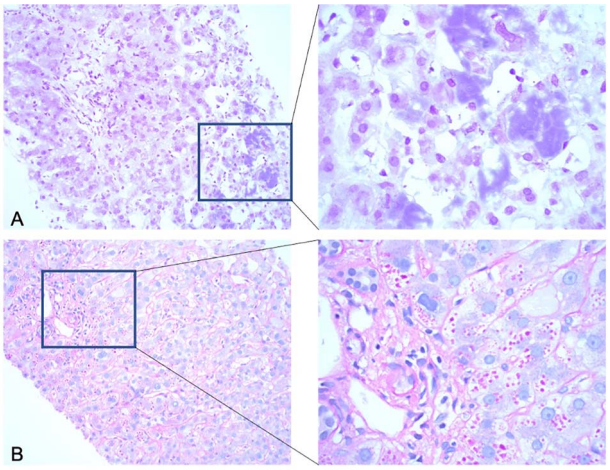

Figure 2. iver biopsy findings with amyloid deposition and A1AT globules. A: Amyloid cytoplasmic deposition within hepatocytes (Crystal violet stain, 200x and 600x) B: Numerous PAS positive diastase resistant globules highlight A1AT globules present in periportal hepatocytes (PASD stain, 200x and 600x).

ATTRwt-CA is considered a rare disease by FDA definition (<200 000 affected individuals), it is not as rare as once reported [4]. Thus, providers may encounter ATTRwt-CA in the context of other truly rare diseases. Additionally, while ATTRwt-CA is a progressive disorder, therapy is most effective when administered before significant cardiac dysfunction and has been demonstrated to prolong survival. [5]. Accordingly, as patients live longer with ATTRwt-CA and ATTRv disease, clinician should expect presence of other non-cardiovascular conditions in affected patients.

The presence of signs of right HF, absence of stigmata of chronic liver disease on clinical exam and absence of portal hypertension on liver imaging and elevated NT-proBNP suggest congestive hepatopathy, but confirmation of cirrhosis and the underlying cause of liver disease should rely on diagnostic tools including liver biopsy and hepatic venous pressure gradients [6].

A1AT-D is an autosomal co-dominant genetic disorder with PiMZ genotype affecting up to 4% of population of European descent. Population-based data suggest that MZ subjects have an increased risk of obstructive lung disease, particularly in smokers. The risk of cirrhosis in MZ subjects is increased in presence of coexisting conditions, such as nonalcoholic fatty liver disease, alcohol misuse and cystic fibrosis. Pulmonary disease susceptibility is partly due to lower circulating levels of A1AT along with inadequate protection of the secreted A1AT against neutrophil elastase mediated lung tissue damage; liver disease susceptibility is due to accumulation of misfolded A1AT protein within the hepatocyte. Screening including pulmonary function testing and liver elastography is recommended in carriers, and intervals for follow-up determined by risk factors. Firm recommendations for screening of all first-degree relatives for A1AT-D exist [7, 8].

Classic hereditary hemochromatosis (HH) is inherited in an autosomal-recessive fashion and all first-degree relatives should be screened for this familial disorder.

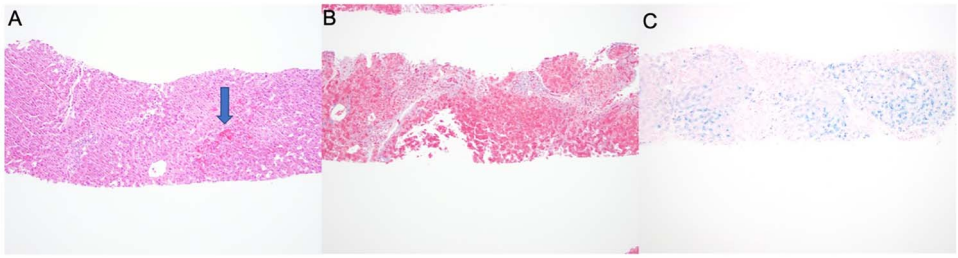

Figure 3. iver biopsy findings with bridging fibrosis in setting of cardiac sclerosis and marked hemosiderosis with HH. A. Liver biopsy shows dilated sinusoids and mild congestion (arrow) (hematoxylin and eosin, 10X). B. bridging fibrosis (Masson's trichrome stain, 10X) C. Iron stain shows grade 4 of 4 hepatocyte iron (Perl's iron, 10X).

The penetrance for developing clinically significant iron overload is rare among patients with C282Y homozygosity genotype (0.5–2%) unless cofactors such as alcohol or HCV are involved. The prevalence of this mutation is ∼2–4% among patients of northern European origin. The primary defect in HFE-related HH is an increase in intestinal iron absorption relative to body iron stores that results in excessive iron deposits in the liver, heart, joints, skin, pancreas and other endocrine organs. Characteristic iron test results in patients with typical HH include an elevation in transferrin saturation (>45%) and an elevation in serum ferritin level. Weekly therapeutic phlebotomy is continued until the patient's serum ferritin level is below 50 ng/ml and the transferrin saturation is below 50%. Approximately 6–10% of patients with HH and cirrhosis develop hepatocellular carcinoma [9]. Interestingly, there is a high rate of HFE mutations in patients with A1AT-D-related cirrhosis and data support the potential for the HFE gene to be a modifier of A1AT-D-related Z protein induced toxicity [10], emphasizing the need for thorough evaluations for all potential etiologies for liver disease in this patient population.

CONCLUSIONS

ATTRwt-CA is an increasingly recognized cause of HFpEF. As demonstrated by these two cases, the presence of comorbid liver disease in patients with ATTRwt-CA suggests that unlike lightning striking twice, clinicians will increasingly encounter older adults with ATTRwt-CA and other diseases that can cause organ dysfunction. Therefore, a high index of suspicion for non-amyloid causes of liver disease is useful, as is active engagement of subspecialists.

ACKNOWLEDGEMENTS

None.

Conflict of Interest statement

No conflicts of interest.

Funding

Dr. Maurer receives grant support from National Institutes of Health (R01HL139671, R21AG058348 and K24AG036778). He has had consulting income from Pfizer, Inc., Eidos Therapeutics, Prothena Corporation Plc, Akcea Therapeutics and Alnylam Pharmaceuticals, and his institution received clinical trial funding from Pfizer, Prothena, Eidos and Alnylam. Dr. Goldklang has received consulting income from Vertex Pharmaceuticals and Takeda Pharmaceuticals, and her institution has received clinical trial funding from Vertex, Grifols International SA, CSL Behring and Arrowhead Pharmaceuticals. Dr. Griffin has had consulting income from Eidos. The remaining authors have nothing to disclose.

Ethical approval

Not applicable.

Consent

Informed patient consents were obtained as per ICMJE guidelines.

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