Circulation: Heart Failure

IMAGES AND CASE REPORTS IN HEART FAILURE

Unmasking Early Wild-Type Transthyretin Amyloidosis Cardiomyopathy in a Patient With Refractory Atrial Fibrillation and Unremarkable Cardiac Imaging

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A 78-year-old man with atrial flutter/fibrillation unresponsive to 3 cardioversions, 1 flutter, and 2 left atrial ablations, myocardial infarction in 2000 treated with a stent to the left anterior descending coronary, hypertension, bilateral carpal tunnel surgery (15 years before), and lumbar spinal stenosis presented with anemia in March 2015. He also complained of dysphagia and was referred for an esophagogastroduodenoscopy. Esophageal biopsies revealed esophagitis. The submucosal vessels in both the duodenal and gastric biopsies showed the presence of a slight thickening by acellular eosinophilic material that raised the possibility of amyloid on routine hematoxylin and eosin–stained slides (Figure [A] and [B]). This finding prompted investigation with Congo red stain, which demonstrated gastric and duodenal amyloid deposition within the submucosal blood vessels.

He was referred to the Utah Amyloidosis Program for further evaluation. His hematologic workup was unimpressive with κ free light chains of 2.29 mg/dL (range, 0.33–1.94 mg/dL), λ free light chains of 2.31 mg/dL (range, 0.57–2.63 mg/dL), κ/λ free light chain ratio of 0.99 (range, 0.26–1.65), serum protein electrophoresis with slight β-γ bridging, and immunofixation showed polyclonal increase in IgA, without monoclonal proteins seen; a bone marrow biopsy was deferred. His renal evaluation demonstrated normal renal function with a creatinine of 1.01 mg/dL, blood urea nitrogen of 15 mg/dL, calculated glomerular filtration rate of 71 mL/min per 1.73 BSA, and no proteinuria. His cardiac studies revealed troponin I of 0.01 ng/mL (range, 0.00–0.03 ng/mL), NT-proBNP (N-terminal pro-B-type natriuretic peptide) of 478 pg/mL (range, 0–449 pg/mL), transthoracic echocardiogram with septal wall thickness of 1.1 cm, posterior wall thickness of 0.9 cm, left ventricular systolic function of 70%, longitudinal strain of –22.3%, relative apical longitudinal strain of 0.71 (normal range, <1.0), and pseudonormal pattern of left ventricular filling (Figure [C]). Cardiac magnetic resonance was negative for infiltrative cardiomyopathy by late gadolinium enhancement and normal left ventricular mass of 109 g (range, 92–176 g) with a mild increase in septal wall thickness of 1.4 cm (Figure [D]). A 12-lead ECG demonstrated atrial fibrillation with minimal criteria for left ventricular hypertrophy and nonspecific ST-T changes (Figure [E]).

Further testing of the duodenal biopsy by mass spectroscopy detected a peptide profile consistent of wild-type amyloid transthyretin amyloidosis (ATTR). To confirm this result and to detect cardiac involvement, the patient underwent endomyocardial biopsy, despite the lack of infiltrative features in the echocardiogram, cardiac magnetic resonance, and biomarkers. The heart biopsy confirmed the presence of interstitial and vascular ATTR amyloidosis (Figure [F] and [G]). Genetic testing was negative for transthyretin mutations. Based on the above studies, the patient was diagnosed with wild-type ATTR amyloidosis with cardiac and gastrointestinal involvement. He was treated with the transthyretin stabilizer diflunisal 250 mg BID.

Key Words: aged ■ amyloidosis ■ atrial fibrillation ■ humans ■ prealbumin

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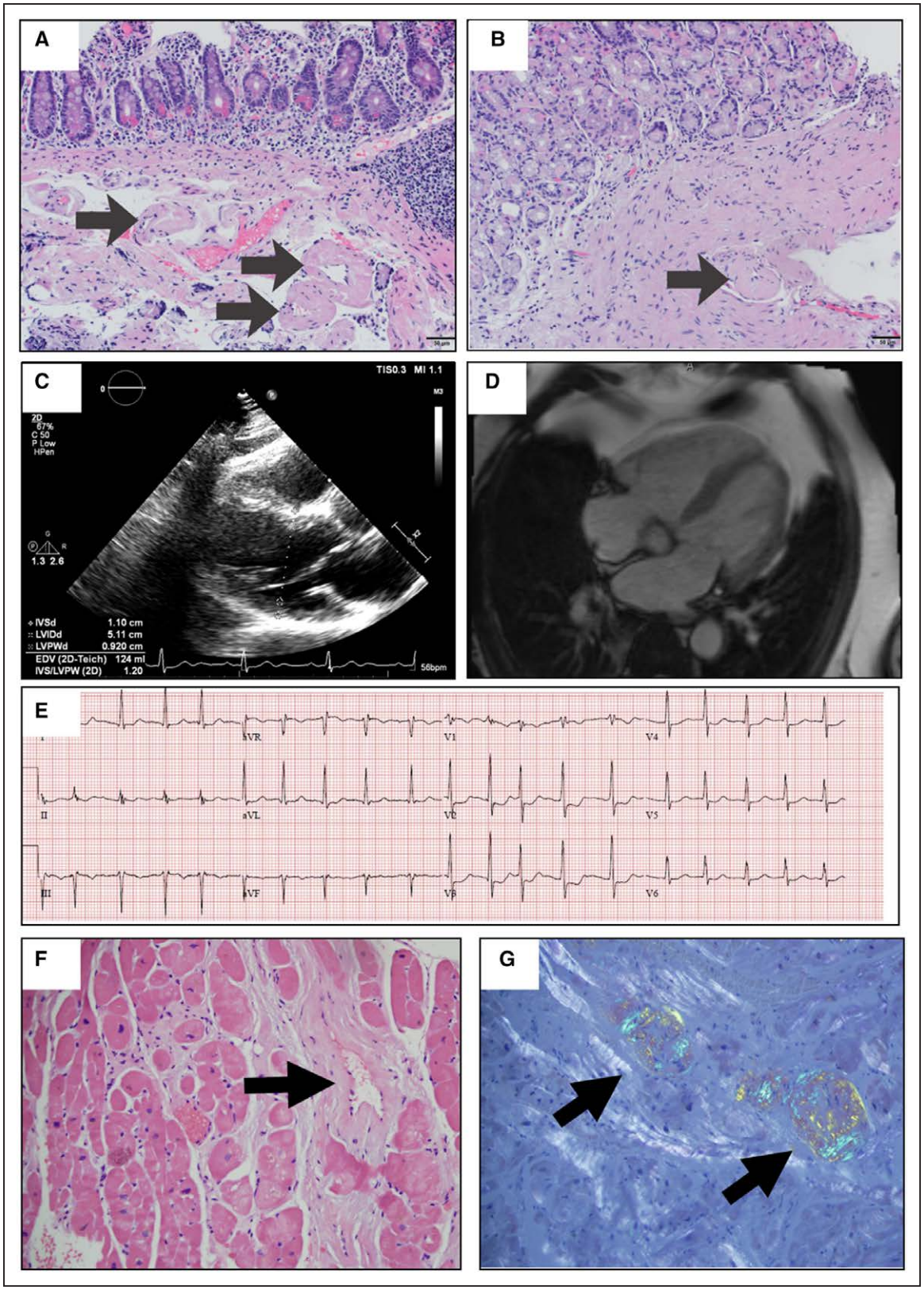

Figure. Patient with wild-type cardiac amyloidosis.
A, Duodenal submucosa with abnormal vessels that appear thickened by waxy, eosinophilic amorphous material suggestive of amyloid. **B**, Gastric biopsy with abnormal vessels within the muscularis mucosae wherein the vessels appear thickened by waxy, eosinophilic amorphous material suggestive of amyloid. **C**, Transthoracic echocardiogram in the parasternal view demonstrates septal thickness of 1.1 cm and posterior wall thickness of 0.9 cm. **D**, Cardiac magnetic resonance with septal thickness of 1.4 cm. **E**, 12-lead ECG shows atrial fibrillation, mild criteria for left ventricular hypertrophy, and nonspecific ST-T changes. **F**, Hemotoxylin and eosin–stained section of myocardium shows small arteries (black arrow) with pale glassy material within the wall. There is focal myocyte hypertrophy and interstitial fibrosis. **G**, Congo red stain under polarized light demonstrates characteristic apple-green birefringence of amyloid material in small arteries (black arrows).

DISCUSSION

This case demonstrates that there are patients with early cardiac amyloidosis (CA) whose diagnosis may be missed because of the absence of typical infiltrative features in cardiac magnetic resonance imaging, echocardiography, electrocardiography, and cardiac biomarkers. For the diagnosis of CA, previous studies have reported a sensitivity of 85% and specificity of 92% with gadolinium enhancement by cardiac magnetic resonance[1]; and a sensitivity of 93% and specificity of 82% using relative apical longitudinal strain by echocardiography.[2] Despite the relatively high diagnostic accuracy of these tests, CA can be missed by conventional techniques and remains underdiagnosed in earlier stages. It seems that lately CA is being suspected and worked up more frequently in patients with cardiac symptoms. For instance, González-López et al[3] reported on amyloidosis being detected in 13% of their patients with heart failure with preserved ejection fraction. Wild-type ATTR predominantly affects the cardiac, neurological, gastrointestinal, and renal systems, and based on the Transthyretin Amyloidosis Outcomes Registry, the most common symptoms include heart failure, 87%; arrhythmias, 65%; carpal tunnel, 33%; numbness, 22%; and dizziness, 20%.[4]

Endomyocardial biopsy is currently the gold standard for diagnosing CA but is not always practical because of its invasive nature and limited availability. Novel noninvasive tests are emerging as potential tools for earlier diagnosis. In 2016, a group of international investigators reported a sensitivity of 74% and specificity of 100% to diagnose cardiac ATTR amyloidosis using a grade 2 or 3 myocardial uptake on bone scintigraphy in the absence of a monoclonal protein.[5] Our patient presented in 2015 when this approach was not yet validated; however, it could have been of potential utility during the initial evaluation. The recent commercial availability of pulse sequences and postprocessing software facilitates the use of cardiac magnetic resonance imaging parametric mapping techniques to enable earlier diagnosis. Noncontrast, native T1 mapping has a reported sensitivity of 92% and specificity of 91%.[6] In addition, extracellular volume as assessed by postcontrast T1 mapping correlates with amyloid burden and may be useful in both detection and in tracking response to therapy. Both native T1 and extracellular volume become abnormal before being able to detect late gadolinium enhancement and should enable earlier detection of amyloidosis. Novel noninvasive tests could potentially be used to screen broader populations in which initial conventional evaluations could miss CA, such as patients with atrial fibrillation, especially if they have other known symptoms associated with amyloidosis like heart failure, bilateral carpal tunnel, or neuropathy.

ARTICLE INFORMATION

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Disclosures

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