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Case Report

Histologic Diagnosis of Coronary Amyloidosis Using Percutaneous Transluminal Directional Atherectomy

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Cardiac amyloidosis (CA) is a cardiomyopathy that results from deposition of amyloid fibrils in cardiac tissue, causing progressive heart failure.[1] Two types of amyloid protein are major causes of CA: light chain amyloidosis and transthyretin amyloidosis (ATTR).[1] In ATTR amyloidosis, dissociation of transthyretin (TTR) tetramer into misfolded monomers leads to self-assembly and formation of insoluble cross-β-sheet-rich amyloid fibrils.[1] Ischemic heart disease is among the comorbidities associated with ATTR-CA. Amyloid accumulation in intramural coronary arterioles associated with microvascular dysfunction is known to occur,[2] but amyloid vasculopathy in epicardial coronary primary arteries causing myocardial ischemia has not been reported.

An 81-year-old man was referred to our hospital for symptomatic heart failure of New York Heart Association functional class III. He had undergone surgery for bilateral carpal tunnel syndrome 7 years earlier. He had been prescribed diuretics for lower-leg edema for 5 years. His leg edema and dyspnea on exertion gradually progressed. At presentation to our hospital, his blood pressure was 105/80 mm Hg, and his heart rate was 73 beats per minute. Physical examination revealed normal heart sounds, clear respiratory sounds, and bilateral leg edema. Chest X ray showed a normal cardiac silhouette without pleural effusion. Electrocardiography showed sinus rhythm with poor R wave progression in leads V1 through V3. His B-type natriuretic peptide level was 68.5 pg/mL (normal range: 0-18.4 pg/mL), and his troponin T level was 0.053 ng/mL (normal: < 0.014 pg/mL). Immunoelectrophoresis of serum and urine proteins was negative for M-protein and Bence-Jones protein. His serum kappa: lambda free light chain ratio was within normal range, at 1.58. Echocardiography demonstrated hypertrophy of the left ventricle (interventricular septum, 12 mm; posterior wall, 13 mm), right ventricle, and interatrial septum, with myocardial granular sparkling (Supplemental Fig. S1). Two-dimensional speckle tracking demonstrated decreased global longitudinal strain with apical sparing. Wall-motion abnormality was also observed at the left ventricular anteroseptal region, with a left ventricular ejection fraction of 55%. Cardiac magnetic resonance imaging showed diffuse late gadolinium enhancement with subendocardial predominance (Supplemental Fig. S2). ^{99m}Technetium-pyrophosphate scintigraphy imaging showed enhanced myocardial uptake (Supplemental Fig. S3). Endomyocardial biopsy demonstrated amyloid accumulation in the myocardial tissue that was positive for TTR and negative for amyloid A, kappa chain, and lambda chain (Fig. 1, A-D; Supplemental Fig. S4). He did not have TTR gene mutation. Based on these findings, he was diagnosed with wild-type ATTR-CA. Even though he did not experience an angina-like episode, left ventricular regional wall-motion abnormality suggested ischemic heart disease comorbidity. Coronary angiography revealed a severely stenotic lesion in the proximal left anterior descending artery, with a resting full-cycle ratio (RFR, a nonhyperemic index assessing functional myocardial ischemia) of 0.83, suggesting significant myocardial ischemia (Fig. 1E). Considering the coronary flow-based ischemic finding and the left ventricular hypokinesia at the left anterior descending territory, we performed percutaneous

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Novel Teaching Points

- Coronary amyloidosis has been reported to occur in the intramural small arterioles as microangiopathy. This case was the first demonstrating accumulation of amyloid fibrils in coronary arteriosclerosis causing luminal stenosis in epicardial primary coronary arteries. Pathophysiological relevance of amyloid accumulation in the development of arteriosclerosis associated with cardiac amyloidosis was suggested.
- Antemortem diagnosis of coronary amyloidosis in primary vessels is quite difficult. Biopsy using percutaneous directional coronary atherectomy enables histologicdiagnosis of coronary amyloidosis in patients with cardiac amyloidosis.

coronary intervention. Intravascular ultrasound and optical coherence tomography demonstrated a homogenous fibrotic or fibrofatty-like plaque (Fig. 1, F and G). The atheromatous plaque pattern was not typical. We resected the coronary artery plaque using a directional coronary atherectomy (DCA) catheter, so as to avoid plaque shift and subsequent side branch occlusion,[3] and we deployed a drug-eluting stent (Fig. 1H; Supplemental Fig. S5). Histopathologic examination of the resected plaque showed an intimal tissue with fibrosis and hyalinization (Fig. 2A; Supplemental Fig. S6). Masson's trichrome staining showed brilliant blue fibrosis and amorphous bluish-gray components suggestive of amyloid (Fig. 2B). Direct fast scarlet (DFS) staining failed to show clear red amyloid deposition under ordinary light microscopy (Fig. 2C); however, polarized light microscopy demonstrated apple-green birefringence, indicating amyloid infiltration in the coronary plaque (Fig. 2D). Furthermore, electron microscopy detected an accumulation of 10-nm-thick amyloid fibrils in the coronary artery plaque (Fig. 2E). Thus, the diagnosis of coronary amyloidosis was established.

He was discharged well, and disease-modifying therapy with tafamidis was commenced at our outpatient clinic.

Discussion

Infiltration of amyloid protein in CA occurs primarily in the myocardial interstitium and conduction system, causing cardiac hypertrophy and arrhythmia. Previous reports of coronary amyloidosis have shown deposition of amyloid fibrils in intramural small arteries, causing so-called intramural coronary amyloidosis.[2,4] Such amyloid microangiopathy leads to wall thickening and luminal occlusion causing coronary microvascular dysfunction and myocardial ischemia.[2] The degree of vascular involvement reportedly is much greater in cardiac light chain amyloidosis than it is in

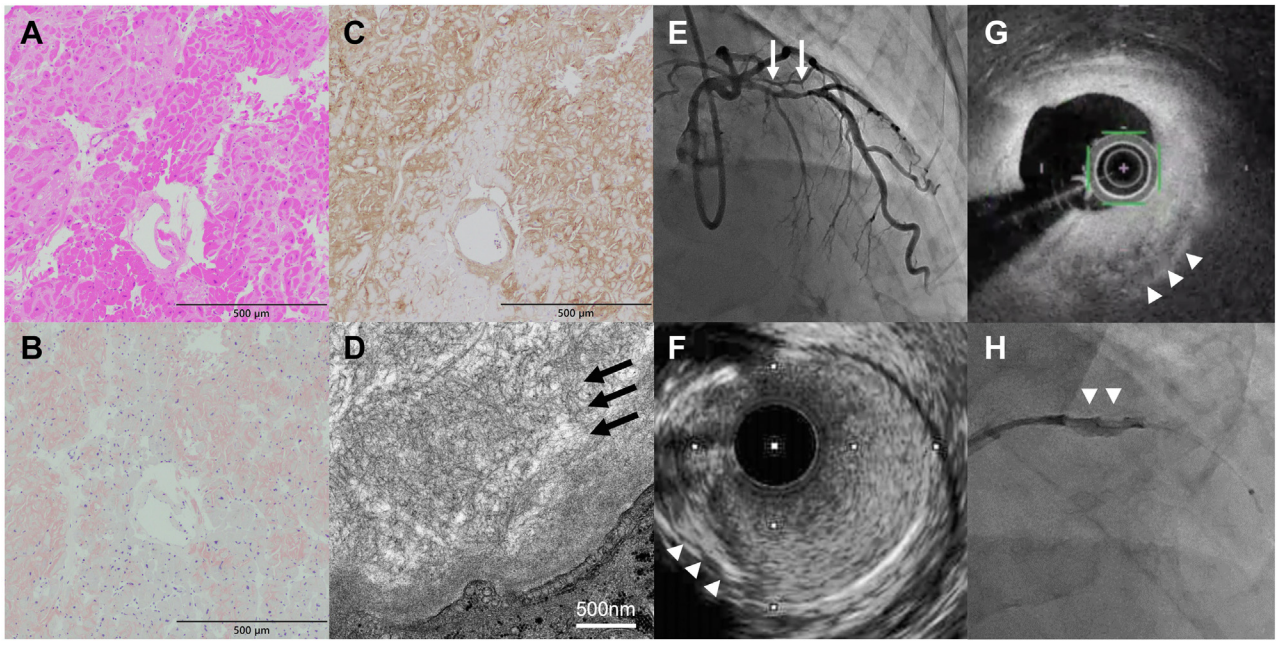

Figure 1. Histopathologic findings of myocardial tissue, and coronary angiographic and intravascular modality images. Right ventricular tissues were obtained by endomyocardial biopsy. (**A**) Hematoxylin-eosin staining. Eosinophilic amorphous substances suggesting amyloid were accumulated in the myocardial interstitium. (**B**) Direct fast scarlet (DFS) staining detected diffuse amyloid deposition in the myocardium. (**C**) Immunostaining against transthyretin. (**D**) Electron microscopy detected infiltration of amyloid fibrils surrounding cardiomyocytes (**arrows**). (**E**) Coronary angiography demonstrated severe stenosis in the proximal left anterior descending artery (**arrows**). (**F**) Intravascular ultrasound imaging of the coronary artery plaque. Mild calcification was observed (**arrowheads**). (**G**) Optical coherence tomography imaging showed a plaque composed mainly of fibrous tissue with a low signal-intensity region (**arrowheads**), suggesting fibro-fatty plaque. (**H**) Coronary artery plaque was resected using directional coronary atherectomy catheter (**arrowheads**) before stenting.

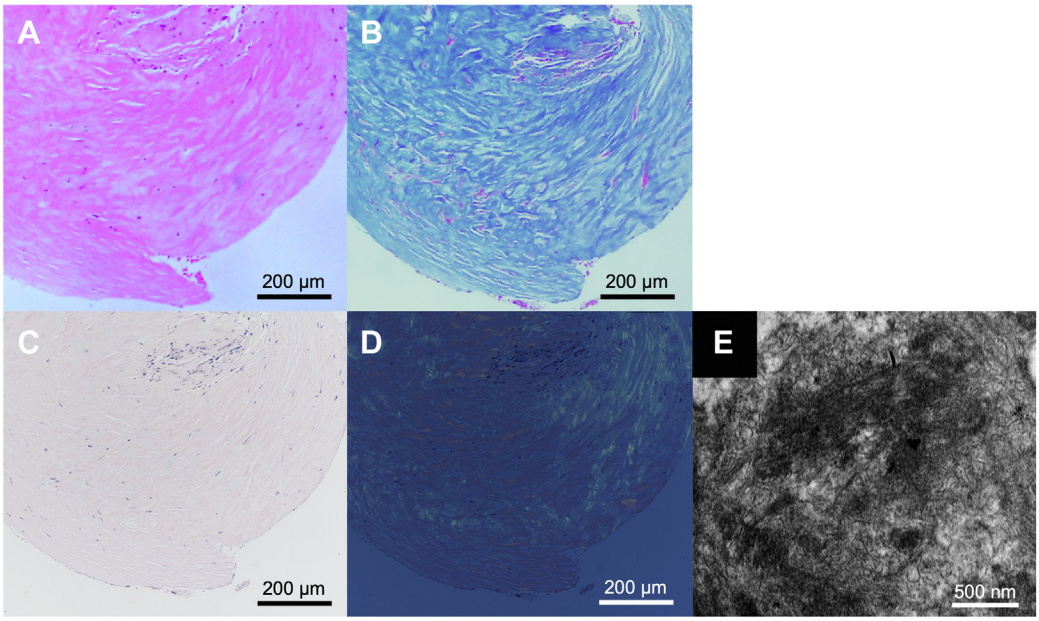

Figure 2. Coronary histologic finding of the resected plaque tissue. (**A**) Hematoxylin-eosin staining of the resected plaque tissue. The plaque was composed of fibrous tissue without the typical finding of a large amount of cholesterol accumulation and foam cell formation. (**B**) Masson's trichrome staining of the plaque tissue. (**C**) Direct fast scarlet (DFS) staining of the coronary plaque tissue. (**D**) Polarized light microscopy of the DFS staining specimen detected apple-green birefringence indicating amyloid deposition in the coronary plaque. (**E**) Electron microscopic finding of the resected plaque tissue. Greyish amorphous fibrillar substances were observed. The fiber thicknesses are approximately 10 nm, compatible with amyloid fibrils.

ATTR-CA. Amyloid deposition in the epicardial coronary arteries has also been demonstrated in a study based on pathologic specimens collected at autopsy and heart transplantation, with highly frequent involvement of adventitial vasa vasorum (up to 91%-97%), but no substantial luminal stenosis was observed in the epicardial coronary arteries.[5]

Our case was the first demonstrating the accumulation of amyloid fibrils in a severely stenotic coronary lesion obstructing an epicardial primary vessel. We successfully established a diagnosis of coronary amyloidosis based on biopsy of the coronary plaque using a DCA catheter, although an antemortem diagnosis of coronary amyloidosis is quite difficult. Whether the coronary artery disease was attributable to coronary amyloid accumulation or whether amyloid deposition occurred in a pre-existing atherosclerotic plaque in the present case remains unclear. However, a reasonable speculation is that amyloid depositions might have accelerated arteriosclerosis through amyloid-triggered inflammation— taking into account a study demonstrating that plasma levels of proinflammatory interleukin-6 were elevated in patients with ATTR-CA, and clinical evidence showing that IL-6 independently predicts future cardiovascular events.[6] A case report has been made of ATTR amyloid accumulation in eccentric intimal thickening of a saphenous vein graft harvested for coronary artery bypass grafting surgery.[7] This observation reinforces our hypothesis that amyloid toxicity plays a role in the development of vascular disease, including arteriosclerosis and vasculopathy. Further longitudinal investigations are needed to determine the pathophysiological role of transthyretin amyloid in the development of coronary artery disease and to demonstrate the effect of ATTR-targeting therapies on plaque regression.

In conclusion, we report a case of ATTR-CA accompanied by stenotic coronary artery plaque, with accumulation of amyloid fibrils in the major branch of coronary arteries. DCA catheter-based biopsy of the coronary plaque contributed to an accurate diagnosis; an antemortem diagnosis was impossible.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.11.009.