A case report of an infiltrative cardiomyopathy in everyday practice: a specific cause that cannot be missed in the elderly

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Background	Transthyretin amyloid cardiomyopathy (ATTR-CM) is a commonly misdiagnosed cardiac condition due to low disease awareness and perceived rarity, which frequently results in incorrect management and poor outcomes. Early and prompt diagnosis has become critical with emerging therapies that improve patient survival.
Case summary	A 68-year-old woman presented to a tertiary care centre with acute decompensated heart failure following recurrent hospitalizations for the same issue over the past several months. Transthoracic echocardiography revealed severe concentric left ventricular hypertrophy with grade III diastolic dysfunction. However, QRS voltage by 12-lead electrocardiogram (ECG) was discordant with the degree of left ventricular hypertrophy seen by echocardiography, and the patient had recurrent non-sustained ventricular tachycardia that necessitated implantable cardioverter-defibrillator implantation a few months prior. After aggressive diuresis, the patient completed cardiac magnetic resonance imaging that raised concern for cardiac amyloidosis. Subsequent serum and urine protein electrophoresis with associated immunofixation were within normal limits. Finally, ATTR-CM was confirmed by technetium-99m pyrophosphate scintigraphy with plans to initiate tafamidis after genetic testing.
Discussion	Patients >60 years of age with diastolic heart failure phenotypically similar to hypertrophic cardiomyopathy and/or hypertensive heart disease should always be evaluated for ATTR-CM. Features that increase suspicion include discordance between left ventricular wall thickness and ECG voltage, and signs/symptoms of a primary peripheral and autonomic neuropathy. Useful non-invasive diagnostic testing has also made the diagnosis of ATTR-CM inexpensive and possible without the need for an endomyocardial biopsy. Unfortunately, this patient's diagnosis of ATTR-CM came late in her disease course, which delayed the onset of definitive therapy.
Keywords	Amyloidosis • Cardiac magnetic resonance • Cardiomyopathy • Diastolic heart failure

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed condition that results from myocardial deposition of aggregated misfolded transthyretin (TTR), a plasma protein predominantly produced in the liver.[1] The two subtypes of ATTR-CM are the hereditary form (hATTR) due to mutations in the TTR gene, and the more common wild-type, caused by a senile aging process in the wild-type TTR protein that can affect up to 10–15% of older adults with heart failure.[1,2] Due to low disease awareness and perceived

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Learning points

- Transthyretin amyloid cardiomyopathy (ATTR-CM) should be considered in patients with diastolic heart failure associated with increased left ventricular mass and wall thickness in the absence of an obvious cause. The index of suspicion should be raised if there is a discrepancy between wall thickness and electrocardiographic voltage, specific tendon-related injuries, signs/symptoms of a primary peripheral and autonomic neuropathy, and/or conduction disease.
- Cardiac magnetic resonance (MR) imaging with late gadolinium enhancement remains a valuable diagnostic modality in the evaluation of patients with ATTR-CM, even in those with cardiovascular implantable electronic devices. Optimal MR settings and imaging sequences can be used to minimize potential artefacts.
- Nuclear scintigraphy with bone avid tracers has emerged as a useful non-invasive tool to definitively diagnose ATTR-CM in the absence of monoclonal protein (detected by serum kappa/lambda free light chain ratio and immunofixation of serum and urine).
- New therapeutic options with novel mechanisms of action are now available to treat ATTR-CM and slow disease progression as well as improve symptoms. However, these therapies are extremely costly at the present time.

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rarity of ATTR-CM, the diagnosis is often delayed or misdiagnosed, which results in inappropriate treatments for a life-threatening disease that until recently had few definitive therapeutic options.[2] An important paradigm shift has also developed in the diagnosis of ATTR-CM using non-invasive methods, including technetium-labelled cardiac scintigraphy.[3]

Timeline

3 months prior to tertiary care	Recurrent hospitalizations at local community hospitals for acute decompensated heart failure without an established aetiology for the patient's acquired cardiomyopathy. In addition, during one previous hospitalization, an implantable cardioverter-defibrillator is implanted due to recurrent non-sustained (monomorphic) ventricular tachycardia
Day 1	The patient is admitted to a tertiary care centre with acute decompensated heart failure. Subsequent transthoracic echocardiography reveals a small left ventricular cavity due to severe concentric hypertrophy with grade III diastolic dysfunction
Day 3	The patient undergoes a right heart catheterization
Day 11	Cardiac magnetic resonance imaging with late gadolinium enhancement suggests cardiac amyloidosis with concern for transthyretin amyloid cardiomyopathy (ATTR-CM), given the absence of a monoclonal protein during serum and protein electrophoresis with immunofixation
Day 12	Technetium-99m pyrophosphate scintigraphy demonstrates a heart to contralateral chest wall uptake ratio >1.5, which confirms the diagnosis of ATTR-CM
Day 13	The patient is discharged home euvolemic with follow-up in the Cardiomyopathy Clinic to initiate tafamidis (pending results of genetic testing)

Case presentation

A 68-year-old Caucasian woman was admitted to a tertiary care centre for acute decompensated heart failure after recurrent hospitalizations elsewhere for the same issue. She had a history of hypertension, paroxysmal atrial fibrillation, and coronary artery disease that required percutaneous coronary intervention of the proximal left anterior descending artery in the remote past. On presentation, the patient reported worsening dyspnoea, weight gain, bilateral lower extremity oedema, orthopnoea, and paroxysmal nocturnal dyspnoea. Initial vital signs included an oral temperature of 36.9°C, heart rate of 87 b.p.m. with a blood pressure of 101/75 mmHg, and a respiratory rate of 22 breaths/min with an oxygen saturation of 97% while on byway positive airway pressure. Physical exam was significant for a S3 gallop, markedly elevated jugular venous pressure, and bibasilar crackles. Chest X-ray revealed pulmonary oedema, and B-type natriuretic peptide level was elevated to 3206 pg/mL. High-sensitive cardiac troponin T levels were persistently elevated (without a significant rise or fall) in the range of 400 ng/L. Her serum creatinine was slightly elevated (1.29 mg/dL) as was her BUN (45 mg/dL), and the complete blood count was significant for an iron-deficiency anaemia with a haemoglobin of 10.8 g/dL and mean corpuscular value of 81.8 fL (white blood cell count 8.6 K/mm^3, platelet count 253×10^3/μL). The hepatic function panel revealed hypoalbuminaemia (2.2 g/dL), but otherwise did not show any significant abnormality (total protein 6.2 g/dL, alkaline phosphatase 150 U/L, aspartate transaminase 29 U/L, alanine transferase 23 U/L, and total bilirubin 0.9 g/dL). Transthoracic echocardiography (TTE) revealed grade III diastolic dysfunction with biatrial enlargement and severe concentric left ventricular hypertrophy (17.8 mm in thickness). Left ventricular systolic function was normal with a calculated ejection fraction of 55%. Twelve-lead electrocardiogram (ECG) was notable for normal QRS voltage. Two months prior at another hospital, the patient underwent placement of an implantable cardioverter-defibrillator (ICD) due to recurrent episodes of non-sustained (monomorphic) ventricular tachycardia. Per chart review, the patient had no history of sudden cardiac death or sustained ventricular tachycardia. She also had not undergone an electrophysiology study to induce ventricular tachycardia/fibrillation prior to ICD implantation. Recent coronary angiography demonstrated no significant progression in coronary artery disease, and no family history of heart failure or sudden cardiac
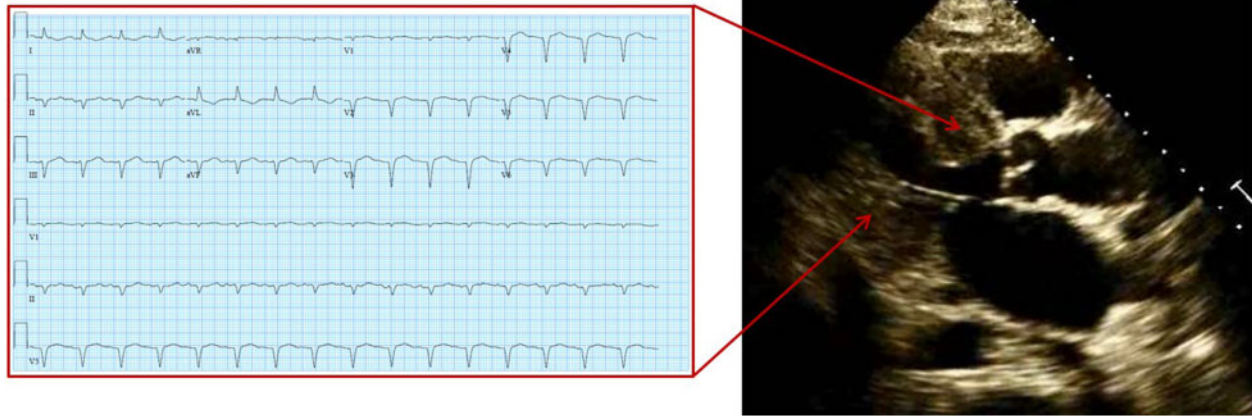
Figure 1 Electrocardiogram and echocardiography. The voltage present on the patient's 12-lead electrocardiogram is discordant with the degree of concentric left ventricular hypertrophy seen by transthoracic echocardiography in the parasternal long-axis view.

death was identified. Indeed, the indication for ICD was certainly in question based on available medical records.

With the above information in mind for this patient, the differential diagnosis for heart failure with concentric left ventricular hypertrophy focused on genetic and acquired primary cardiomyopathies. Genetic considerations included neutral septum hypertrophic cardiomyopathy, mitochondrial myopathies, and glycogen storage diseases (e.g. Fabry disease, Danon disease). Given the patient's age, acquired primary cardiomyopathies seemed more likely. Her recent history of ICD implantation due to recurrent non-sustained ventricular tachycardia raised concern for an infiltrative process, such as light chain amyloid or ATTR-CM. Additionally, the voltage on her 12-lead ECG was discordant with the degree of left ventricular hypertrophy seen by TTE (Figure 1). Hypertensive heart disease seemed less likely as well, given the patient had well-controlled blood pressure without anti-hypertensive therapy throughout her hospitalization.

Initially, the primary focus in patient management was to promptly address her acute decompensated heart failure. As her physical exam was consistent with a low-output cardiac state with fluid overload, she was placed on a low-dose dopamine infusion (5 µg/kg/min) prior to TTE to help augment diuresis. However, in the setting of a small left ventricular cavity (as discovered later by cardiac imaging), the patient became hypotensive with the resulting decrease in stroke volume from the calcitropic properties of dopamine that increase contractile function. Dopamine was subsequently discontinued, and the patient underwent aggressive intravenous diuresis with loop diuretics alone directed by a Swan-Ganz pulmonary artery catheter. On right heart catheterization, the patient was found to have elevated right- and left-sided filling pressures with a mean right atrial pressure of 11–13 mmHg and a mean pulmonary capillary wedge pressure of 25 mmHg (respectively), in addition to mild pulmonary hypertension (40/22/30 mmHg). Her cardiac output and index (3.43 L/min; 1.72 L/min/m^2) were diminished as well.

After undergoing appropriate reduction in left ventricular preload, the patient completed cardiac magnetic resonance (MR) imaging with late gadolinium enhancement (LGE). This study revealed concentric left ventricular hypertrophy (measuring up to 2.3 cm in the inferoseptum) as well as right ventricular hypertrophy, biatrial enlargement, and a diffuse pattern of patchy mid-myocardial delayed enhancement within the left ventricle; findings all consistent with cardiac amyloidosis. Other supporting evidence of cardiac amyloidosis by cardiac MR included a small pericardial effusion, bilateral pleural effusions, and—most importantly—reverse nulling of the myocardium with inability to fully null the myocardium. To differentiate between TTR cardiac amyloidosis and the light chain type, serum and urine protein electrophoresis with associated immunofixation were obtained. Subsequent results did not reveal a monoclonal protein consistent with light chain amyloidosis. Therefore, the patient underwent technetium-99m pyrophosphate (Tc-99m-PYP) scintigraphy to confirm ATTR-CM. This evaluation demonstrated mild diffuse radiotracer uptake in the myocardium with additional focal elevated activity worse in the anterolateral wall of the left ventricle (Figure 2). The heart to contralateral chest wall uptake ratio was >1.5, which has a specificity of 99% for ATTR-CM.[2]

Following hospital discharge, arrangements were made for the patient to establish care in the Cardiomyopathy Clinic, where she was to initiate tafamidis *after* genetic testing. Genetic testing was negative for a TTR gene mutation and so the wild-type form of ATTR-CM was confirmed. Due to a late presentation in the patient's disease course, orthotopic heart transplant was considered as well.

Discussion

Patients with ATTR-CM most commonly present with diastolic heart failure and left ventricular wall thickness ≥14 mm. Important associated symptoms include polyneuropathy or dysautonomia, bilateral carpal tunnel syndrome, spontaneous biceps tendon rupture, and lumbar spinal stenosis; all of which are related to amyloid deposition.[1,2] Electrocardiogram may show signs of atrioventricular block, atrial arrhythmias (e.g., atrial tachycardia and atrial fibrillation/flutter),
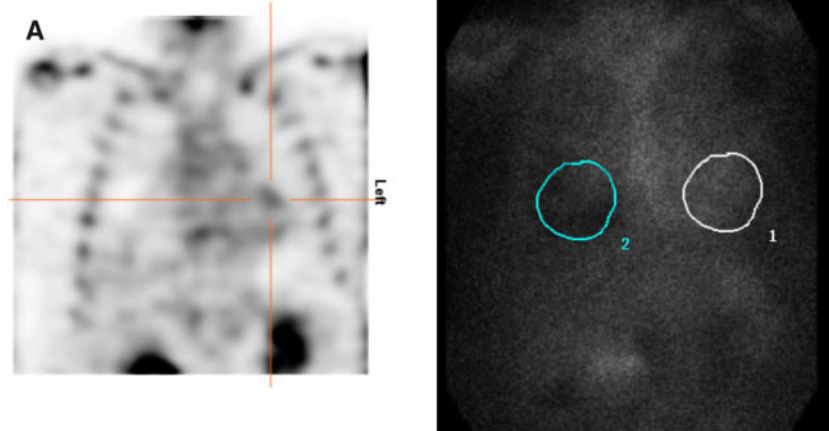
Figure 2 Bone scintigraphy. (*A*) Anterior planar images from the patient's Tc-99m PYP scintigraphy demonstrating clear evidence of cardiac tracer uptake. (*B*) Increased heart to contralateral chest ratio of 1.54.
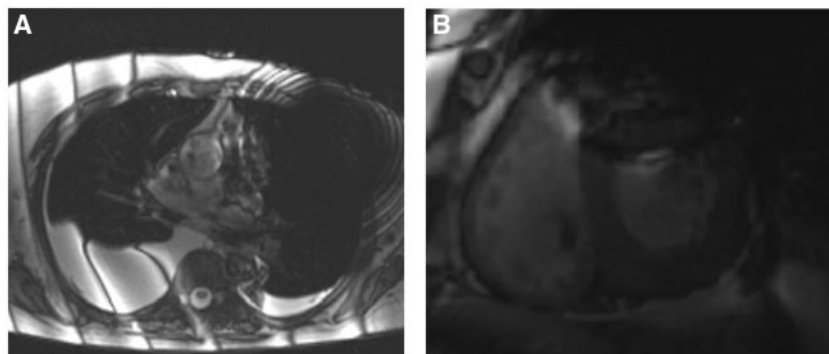

Figure 3 Susceptibility-based artefacts due to implantable cardioverter-defibrillator. (*A*) Magnetic resonance axial view of the heart demonstrating susceptibility-based artefact related to the patient's left-sided implantable cardioverter-defibrillator. There is also incidental note of bilateral pleural effusions, which are frequently seen in patients with cardiac amyloidosis. (*B*) Short-axis FIESTA sequence image demonstrates left ventricular hypertrophy with a basal inferior wall that measures 20 mm in thickness at end-diastole. Again, evaluation is limited by susceptibility-based artefact.

and/or a discrepant QRS voltage in the setting of increased left ventricular wall thickness. These patients may also be at risk for ventricular tachycardia or fibrillation.[1]

Transthoracic echocardiography should be the initial non-invasive test in helping to establish the diagnosis of ATTR-CM due to its relative accessibility and low cost. Frequently, the earliest abnormality is a symmetrically increased left ventricular wall thickness resulting in a non-dilated or small left ventricular cavity with evidence of advanced diastolic dysfunction. On myocardial strain as measured by speckle tracking echocardiography, there is a reduction in longitudinal strain with relative apical sparing (>2:1 apical to basal ratio), which is commonly referred to as the 'cherry on top' pattern.[4] Among patients with undifferentiated left ventricular hypertrophy, this finding can be helpful to distinguish ATTR-CM from other cardiomyopathies and can precede many other TTE findings associated with this diagnosis,

including significant diastolic dysfunction. Indeed, two-dimensional speckle tracking echocardiography may even allow differentiation between the wild-type and mutant forms of ATTR-CM.[5] Unfortunately, this modality could not be used in this patient due to significant beat-to-beat variation in heart rate from frequent atrial and ventricular ectopy, which is an important limiting technical factor in strain assessment. With TTE being an important modality in the evaluation of valvular heart disease, it is also important to consider ATTR-CM in patients with (stage D3) paradoxical low-flow severe aortic stenosis.[2]

After echocardiography raises concern for cardiac amyloid, cardiac MR imaging should be pursued as part of an integrated imaging approach in the evaluation for possible ATTR-CM.[6] In cardiac amyloidosis, MR images show a distinctive pattern of global left ventricular LGE, marked extracellular volume expansion, and an abnormal myocardial nulling time; a combination rarely seen in other
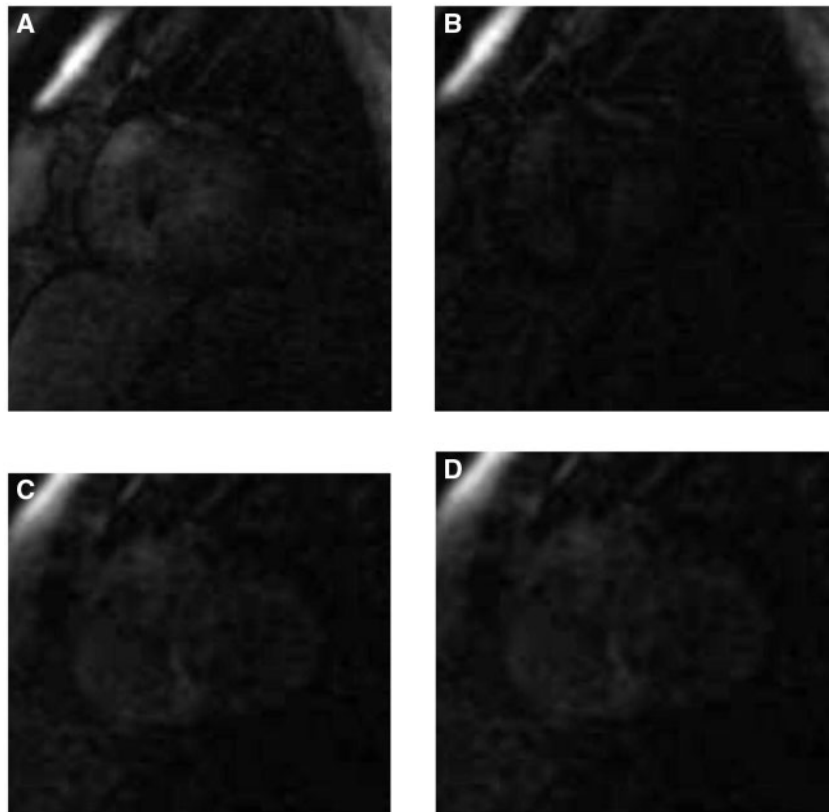
Figure 4 Inability to null myocardium during inversion recovery pulse and late gadolinium enhancement sequences of cardiac magnetic resonance. (A–C) Inversion recovery pulse sequences during cardiac magnetic resonance of the left ventricle in short-axis demonstrate inability to null the myocardium, which is highly suggestive of cardiac amyloidosis. Images are taken at (A) 20 ms, (B) 52 ms (incompletely nulled myocardium), and (C) 125 ms (nulled blood pool). (D) Delayed enhancement sequences during cardiac magnetic resonance also demonstrate an inability to null the myocardium despite multiple attempts.

cardiomyopathies. These distinct features of cardiac amyloid on cardiac MR help distinguish it from hypertrophic phenocopies. The use of gadolinium-based contrast also allows for quantification of myocardial extracellular volume, which is typically 22–28% but can increase to >40% globally with diffuse fibrosis as seen with cardiac amyloid.[7]

In the past, cardiac MR was limited to patients without cardiovascular implantable electronic devices (CIEDs) due to significant susceptibility-based artefacts and safety concerns. In patients with left-sided CIEDs, these artefacts often localize to the anterior and apical myocardial regions (Figure 3) and are more expansive in LGE sequences as compared to cine, T2-weighted, or perfusion imaging sequences.[8] Such artefacts can be reduced by lowering the magnetic field strength and shortening the echo time. In this patient where the benefits of cardiac MR outweighed any risk, the susceptibility-based artefacts were overcome by focusing on the inversion recovery pulse sequences that can be used to null the signal from a desired normal tissue to accentuate surrounding pathology. These sequences, along with LGE analysis, confirmed an inability to null the myocardium due to a high burden of amyloid deposition in this patient (Figure 4). Thus,

cardiac MR with use of appropriate sequences remains a valuable diagnostic modality in patients with suspected ATTR-CM who also have a CIED.

Nuclear scintigraphy using bone avid tracers (Tc-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid, Tc-99m PYP, and Tc-99m-labelled hydroxy-methylenediphosphonate) has recently emerged as an important non-invasive tool for the specific identification of ATTR-CM, and is a critical component of the integrated imaging approach in cardiac amyloid after echocardiography and cardiac MR are completed.[3]Tc-99m-PYP scintigraphy, readily available in the USA, has a higher sensitivity for diagnosing ATTR-CM in comparison with light chain cardiac amyloidosis.[9] Additionally, a positive scan alone has a >99% sensitivity for detecting TTR amyloid deposits.[10] Thus, in the absence of monoclonal protein as detected by serum kappa/lambda free light chain ratio and immunofixation of serum and urine, the definitive diagnosis of ATTR-CM can be obtained without endomyocardial biopsy, the current gold standard.[3]

The importance of early diagnosis of ATTR-CM has grown with a recent phase III trial with tafamidis, a drug that stabilizes the TTR tetramer and may reduce formation of TTR amyloid. Specifically,

among patients with ATTR-CM and New York Heart Association functional class I–III symptoms, tafamidis was found to reduce mortality and cardiovascular-related hospitalizations as well as improve functional capacity and quality of life.[11] Unfortunately, the use of tafamidis (available in two dosage forms) is limited by its high cost, which has a list price per year of $225 000 (US dollars) and is among the most expensive cardiovascular drugs currently available in the US market.[12] Other therapies (including diflunisal, patisiran, and inotersen) are effective for hATTR polyneuropathy, but have limited evidence for improving cardiovascular outcomes and do not have Food and Drug Administration approval yet in ATTR-CM. Finally, ATTR-CM patients with isolated cardiac involvement may benefit from orthotopic heart transplant, which in a very select group of patients can improve survival.[13]

Conclusions

In sum, ATTR-CM should be considered in patients >60 years of age with diastolic heart failure associated with increased left ventricular mass and wall thickness in the absence of an obvious cause. Patients frequently with hypertensive phenocopies have a CIED implanted for a variety of indications, which in the past was a contraindication to cardiac MR with LGE due to safety concerns and susceptibility-based artefacts. However, optimal MR settings and imaging sequences can now be used to minimize potential artefacts, such that this modality can remain a part of the evaluation of ATTR-CM in addition to traditional and speckle tracking echocardiography. Based on results of cardiac MR with LGE and echocardiography, technetium-labelled cardiac scintigraphy can non-invasively confirm the diagnosis of ATTR-CM in the absence of monoclonal protein as detected by serum and urine protein electrophoresis with immunofixation.

Lead author biography

Dr Manoj Kesarwani is a Health Sciences Clinical Assistant Professor at the University of California, Davis School of Medicine. As an interventional cardiologist, Dr Kesarwani has clinical and research interests that focus on the physiologic assessment of coronary stenosis, intracoronary imaging, coronary atherectomy, and complex coronary interventions via a transradial approach. Helping to reduce racial disparities in the management of patients with coronary artery disease is another important research interest in his practice.

In addition, Dr Kesarwani serves as a clinical educator to medical students, internal medicine residents, and general cardiology and interventional cardiology fellows alike.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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