

## Congestive Heart Failure: Think Outside the Box

Joyce Lim<sup>1,4</sup>, Elissa Williams<sup>2</sup>, Peter Braude<sup>1,3</sup> and Seshasayee Narasimhan<sup>1,2,4,5,6\*</sup>

<sup>1</sup>Internal Medicine, Manning Base Hospital, Taree, NSW, Australia

<sup>2</sup>The Heart Centre, Taree, NSW, Australia

<sup>3</sup>Pulmonology, Manning Base Hospital, Taree, NSW, Australia

<sup>4</sup>Cardiology, Manning Base Hospital, Taree, NSW, Australia

<sup>5</sup>Conjoint Senior, University of Newcastle, Callaghan, NSW, Australia

<sup>6</sup>Adjunct Senior Lecturer, University of New England, Armidale, NSW, Australia

\*Corresponding Author: Seshasayee Narasimhan, Cardiology, Manning Base Hospital, Taree, NSW, Australia.

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### Abstract

We present an intriguing case of delayed diagnosis in a 67-year-old male with exertional dyspnoea and chest pain. Following a positive exercise stress test, a coronary angiogram was performed showing a 90% stenosis in the mid third of the posterolateral ventricular branch of the right coronary artery. Despite successful revascularization of the vessel, his exertional dyspnoea continued to worsen. There were multiple hospitalizations for heart failure secondary to left ventricular (LV) systolic dysfunction. This prompted extensive investigations that later revealed cardiac amyloidosis (CA) secondary to multiple myeloma (MM) after two years from symptom onset. This case highlights the substantial challenges contributing to delays in diagnosing CA, which has a median survival time of < 1 year in advanced cases and high risk of sudden cardiac death within 90 days of diagnosis.

**Learning Objective:** CA is a challenging diagnosis due to its rare, variable and non-specific clinical manifestation. This often results in delayed diagnoses. However it is critical to consider CA in the differential diagnosis of unusual presentations of exacerbation of heart failure (HF) due to its associated high morbidity and mortality.

**Keywords:** Congestive Heart Failure; Cardiac Amyloidosis; Multiple Myeloma

### Introduction

We present a case report of a 67 year old male presenting with exertional dyspnoea and chest pain, diagnosed with CA secondary to MM causing LV dysfunction. This case reports highlights the challenges of diagnosing CA in clinical practice. CA is a diagnosis that is frequently missed or delayed because it is a rare condition with vague, variable and non-specific clinical manifestations. It reinforces the need to do away with cognitive biases to broaden the differential diagnoses when challenged with common presenting complaints that do not respond to therapy.

### Case Description

A 67-year-old male presented for an outpatient stress test for exertional dyspnoea and chest pain. The stress test was positive for reversible ischemia (chest pain, dyspnoea and inferior ST depression) and was referred to Cardiology for consideration of an invasive assessment. Of interest is the fact that he had gradually progressive dyspnoea. His medical background included quiescent gout and hypothyroidism. He was a lifelong non-smoker, who could walk 5 km/day. At the time of review, he was dyspnoeic with domestic duties such as mowing the lawn. Besides progressive dyspnoea, he developed a hoarse voice.

Of note, his ECG showed a sinus rhythm, first-degree heart block and non-specific interventricular conduction delay (Figure 1). It did not meet low voltage criteria. His coronary angiogram revealed a dominant right coronary artery with a large right posterolateral ventricular branch (RPLV) with mid third discrete 90% stenosis. His left main and left circumflex coronary arteries had minor luminal irregularities. His left anterior descending coronary artery was small and diffusely diseased. In the proximal third, there was an eccentric and ectatic 50% stenosis. The RPLV was successfully revascularized with a drug-eluting stent (XIENCE ALPINE 3.0 mm x 12 mm). Post procedure, his exertional chest pain was relieved but his dyspnoea continued to cause issues.

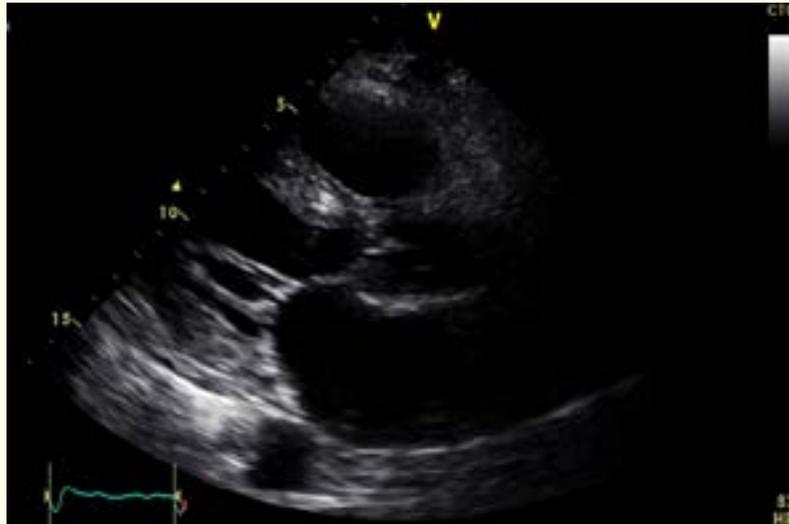


**Figure 1:** ECG showing sinus tachycardia, first-degree heart block and non-specific inter ventricular conduction delay.

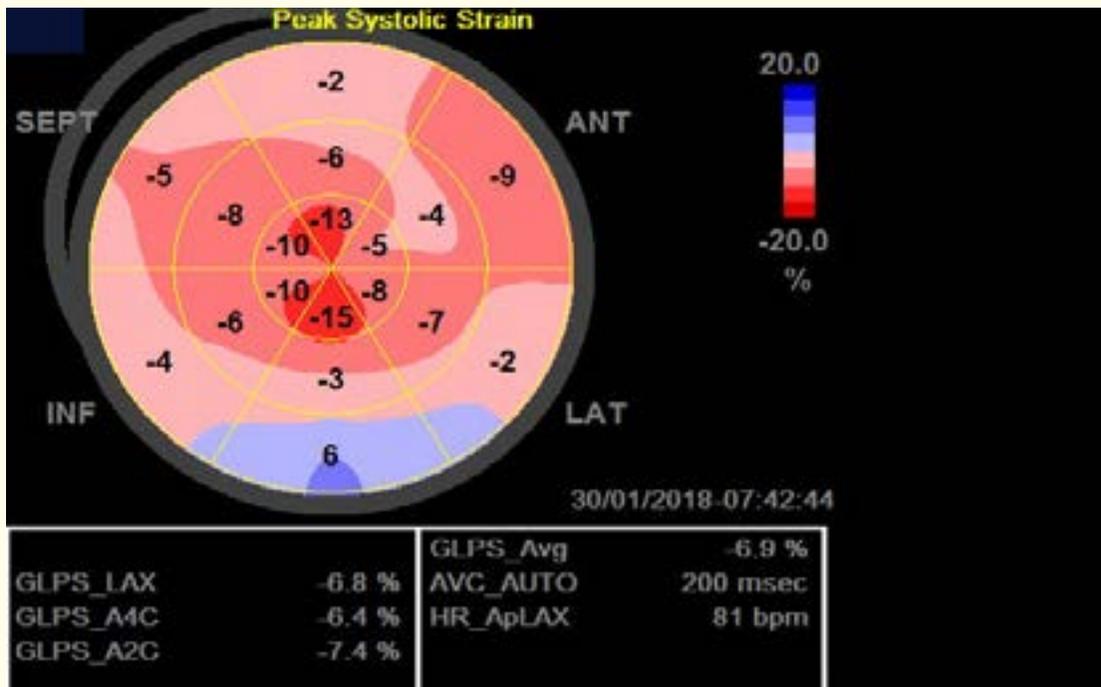
His initial transthoracic echocardiography (TTE) showed a mild to moderate concentric LV hypertrophy with preserved LV ejection fraction and moderate diastolic dysfunction. The E wave velocity was 84 cm/s, E' wave velocity 3 cm/s, A wave velocity 66 cm/s, E/A ratio of 1.27 and E/E' ratio of 28 and a deceleration time of 234 msec. The right ventricle was of normal size and function with a TAPSE of 1.7 cm. Mild bi-atrial enlargement was seen. No granular 'sparkling' appearance of the myocardium was evident. Unfortunately no 2D speckle-tracking strain analysis was performed on the initial echo.

Extra-cardiac causes for his dyspnoea were investigated using a CT chest, pulmonary angiograms and pulmonary function tests. His CT chest and pulmonary angiogram showed normal lung parenchyma with no evidence of pulmonary emboli. Pulmonary function tests showed an FEV1/FVC ratio of 77% with a FEV1 2.63 (84% predicted) and FVC 3.40 (86% predicted) and normal diffusion capacity with a normal KCO. He also had a positive bronchial hypertonic saline provocation test. Nasolaryngoscopy revealed a macroscopically normal upper airway. Despite treatment for asthma, there was no improvement in his symptoms or respiratory parameters on repeat spirometry. On further specialist review, vocal cord dysfunction was clinically diagnosed using the Newcastle laryngeal hypersensitivity questionnaire [1].

Despite a promising diagnosis for his hoarse voice, it failed to explain the development of fluid overload and bilateral pleural effusions with a BNP 1570 ng/L, which was more suggestive of HF. Despite diuresis with frusemide, he remained dyspnoeic, prompting a progress TTE. The TTE performed 6 months after the initial echo showed mild-moderate concentric LV hypertrophy with low-normal LV ejection fraction of ~50% and moderate diastolic dysfunction. E wave velocity was 70 cm/s, E' wave velocity 2 cm/s, A wave velocity of 35 cm/s, E/A ratio of 1.9, and E/E' ratio of 34 and deceleration time 106 msec. The right ventricle was dilated with reduced systolic function with a TAPSE of 1.2 cm. There was moderate bi-atrial enlargement. No granular 'sparkling' appearance of the myocardium was evident (Figure 2). 2D speckle-tracking strain analysis was performed on these echo images, however, only after the diagnosis of CA was considered. The diagnosis was made on clinical suspicion. The strain analysis showed reduced global longitudinal strain without the relatively well-preserved apical strain with significant basal impairment that is seen in CA (Figure 3).



**Figure 2:** 2D Parasternal long axis view of the left ventricular demonstrating mild to moderate concentric increased wall thickness and lack of 'sparkling' appearance of the myocardium.



**Figure 3:** Bulls-eye plot of the peak systolic strain values showing reduced global longitudinal strain.

The diagnosis of CA was confirmed on endomyocardial biopsies staining positively with Congo Red stain for amyloid with focal apple green birefringence. AA amyloid immunoperoxidase stain was negative. No further subtyping of the amyloid deposits was performed.

Primary causes for the CA were sought. Serum electrophoresis and immunofixation showed abnormal M bands in the beta region 22 (5 - 11 g/L) and immune paresis in the gamma region of 4 (7 - 15 g/L). Serum immunofixation electrophoresis and serum free light chains

showed elevated immunoglobulin G of 22.58 g/L (7.00 - 16.00) and kappa free light chains of 1240.00 (6.70 - 22.40 mg/L). Subsequent bone marrow aspirate showed increased plasma cells of 24%. A retrospective review of his blood counts and biochemistry at presentation showed a Hb 143 (130 - 180 g/L) and corrected Ca 2.37 with normal renal functions and ESR. Skeletal survey did not reveal any lytic bone lesions.

### Discussion

It took over two years from symptoms onset to making the unifying diagnosis of IgG MM with secondary CA. Unfortunately, the opportunity to challenge the secondary diagnosis of vocal cord dysfunction was lost as the patient died within a month of his diagnosis. It is possible that he had laryngeal amyloidosis or laryngeal MM. Although rare, both have been previously described to cause a hoarse voice [2,3]. The case highlights the significant diagnostic challenges CA poses resulting in diagnostic delays.

MM and other plasma cell clonal disorders are typically associated with amyloid light chain (AL) CA. The amyloid deposits consist of misfolded immunoglobulin light chains, which deposit in the endomyocardium. This results in biventricular hypertrophy and increased ventricular stiffness leading to HF with preserved ejection fraction. In a subset of patients, HF with reduced ejection fraction occurs in the absence of hypertrophy. This has been attributed to the direct toxic effects of light chains and/or vascular infiltration of amyloid. These infiltrates around the small arterioles supplying the heart will occasionally produce symptoms of angina [4,5].

In a patient survey of 533 participants with AL amyloidosis, diagnosis was not established until  $\geq 1$  year from time of symptom onset in 37.1% of patients. In 16.8% of patients, 4 physician reviews were required prior to a diagnosis and  $\geq 5$  physicians in 31.8% of patients. This is in part related to the low incidence of CA. As a disease entity, AL amyloidosis has an incidence of 8 - 12 per million person years [6]. This is further compounded by its variable clinical manifestations. A study of 341 patients showed that AL amyloidosis could have up to 32 distinct symptoms, which are often non-specific in nature. The two most common symptom being fatigue and dyspnoea [7]. Together these factors significantly contribute to delayed diagnoses.

Clinician factors are often influenced by patient interpretation of their symptoms. Early symptoms are not always of immediate concern to patients because of the non-specificity of symptoms [7]. In our case, his breathlessness was so insidious in progression that a medical review was not sought until he developed significant functional limitations in addition to stable angina.

In addition to clinician and patient factors, the patient never showed typical ECG changes of amyloidosis. The two most common ECG abnormalities being low voltage QRS complexes, defined as  $<5$ mm height in all limb leads and a pseudoinfarct pattern in the precordial leads. The patient, however did have an atrioventricular block, which has been found in 22% of patients with amyloidosis [8].

The atypical findings on ECG were further compounded by the patient's unusual initial TTE findings. From an echocardiography point of view, CA is difficult to diagnose on TTE alone. The characteristic TTE findings for amyloidosis include an increase in wall thickness of the left ventricle and right ventricle; normal LV ejection fraction, which may decrease in the later stages of the disease, diastolic dysfunction, granular, 'sparkling' appearance of the myocardium and bi-atrial enlargement [9]. 2D speckle-tracking strain analysis has been shown to be useful in assessing CA. In CA there is relatively well-preserved apical strain with significant basal impairment [10].

The non-specific symptoms and atypical ECG and TTE findings in the initial stages of the disease, together with patient and clinician factors, make the early diagnosis of CA challenging. With a median survival of  $< 1$  year for advanced CA (Mayo stages IIIa and IIIb) and a 25 - 30% risk of sudden cardiac death  $\leq 90$  days from diagnosis, it is critical to ensure early diagnosis [4]. One needs a high degree of clinical suspicion for CA as part of the differential diagnosis in patients presenting with non-specific common symptoms, who subsequently have abnormal investigations and do not respond to standard therapy.

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