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Suspected Cardiac Amyloidosis in a 67 year Old, Caucasian Female

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INTRODUCTION

Amyloidosis is a rare set of diseases that is characterised by the deposition of pathological amyloid in tissues and/or organs. Amyloid is a proteinaceous substance, 95% of which consists of aggregates of misfolded, insoluble proteins; that make up fibrillar material, and the remaining 5% consists of the P component, (a pentameric protein) and other glycoproteins. The heart is commonly involved in amyloidosis and can occur as part of systemic amyloidosis or as localised disease (Firkle, *et al.,* 2013).

In cardiac amyloidosis, amyloid is deposited in the extracellular space of the heart, resulting in stiffening of the heart, with involvement of both ventricles and atria; as well as the valves, leading to the development of a restrictive cardiomyopathy. Cardiac involvement is associated with a poor prognosis. In the past, the diagnosis of cardiac amyloid was often made during autopsy, (Banypersad, *et al.,* 2012; Falk, *et al.,* 2016); however, advances in cardiac imaging have recently led to increased detection rates (Dungu, 2015).

In this case report, we will describe the presentation, investigation and management of a 67 year old Caucasian female, with suspected cardiac amyloidosis.

Keywords: *'amyloidosis', 'cardiac', 'amyloid', 'cardiac imaging', 'heart'.*

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CASE PRESENTATION

A retired, 67 year old Caucasian, female presented with a 2 week history of increasing lethargy, decreased appetite, and oliguria.

She had a history of diabetes mellitus and diabetes retinopathy, hypertension, chronic kidney disease, cerebrovascular disease with a history of a left frontal lobe infarct, congestive heart failure, depression and dementia. Her medical treatment included Bumetanide, Metformin and Valsartan.

On admission, the patient was noted to be dehydrated, but examination was otherwise unremarkable.

Blood investigations showed a raised Serum Urea (25mmol/L), a raised Serum Creatinine (269 umol/L), and a decreased eGFR (16 mls/min), with a White Blood Cell count of 8.05 x 10^9/L, a Haemoglobin of 11.6 g/dL, and a Platelets count of 369 x 10^9.

She was initially diagnosed with an acute-on-chronic kidney injury, (previous Creatinine was 146 umol/L) and treated with intravenous fluids, with subsequent improvement in urinary output and serum Creatinine.

The patient's condition improved considerably, but while still an in-patient, she developed severe, compressive chest pain and dyspnoea. An electrocardiogram showed T-wave inversion/depression in V5-V6, which was previously documented, and poor R wave progression (Refer to Figure 1). Serial serum Troponin rose from 543-856 ng/L.

Since her D-Dimer level was elevated (231ng/ml), a Lung Perfusion scan was performed, which did not show evidence of a pulmonary embolism. A diagnosis was made of a non-ST elevation Myocardial Infarction (nSTEMI). Consequently, intravenous unfractionated heparin was started, and one unit of packed red cells was also transfused in view of a haemoglobin of 9 g/dL.

Management was conservative, considering that the patient was deemed unfit for dual anti-platelet therapy due to persistent low-grade anaemia. The patient also refused invasive coronary angiography.

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OTHER INVESTIGATIONS

Serum Protein Electrophoresis was within normal limits. Serum free light chains showed elevated Kappa (63.5) and Lambda (30.5) chains (Ratio of 2.08).

JAK2 V617F mutation and BCR/ABL mutation were not detected. Urine for Bence-Jones was also negative. There were no amyloid deposits visible on bone marrow biopsy.

CARDIAC IMAGING INVESTIGATIONS:

Echocardiography showed significant concentric left ventricular hypertrophy, restrictive filling, high filling pressures, decreased longitudinal function with apical sparing, a small pericardial effusion, and severe mitral regurgitation.

Cardiac Magnetic Resonance Imaging (CMR) confirmed the presence of eccentric left ventricular hypertrophy with mildly impaired left ventricular ejection fraction, along with severe hypo-kinesia of the basal to mid-ventricular inferior/infero-septal left ventricular walls (Refer to Figure 2). Severe mitral regurgitation, along with mild pericardial effusion with maximal thickness of 8mm around inferior surface of the heart was also delineated.

Despite the poor-quality scan, due to failure of the patient to breath-hold, the findings were suggestive of dual pathology; that is cardiac amyloidosis and a non-transmural sub-endocardial infarct in inferior/infero-septum. These findings correlated with the findings on echocardiogram described earlier.

A Nuclear Medicine Cardiac Amyloid scan showed minimally increased tracer uptake in the myocardium (Refer to Figure 3). There was no evidence of extra-cardiac amyloid. The mean heart to contralateral ratio (H/CL) was 1.08.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included a non-transmural sub-endocardial infarct in the inferior/infero-septum due to the raised troponin, T wave inversion in V5-V6 and poor R wave progression in an area of left ventricular hypertrophy with a mildly impaired left ventricular ejection fraction. Unfortunately, in this case, the patient did not undergo coronary angiogram to rule out the above diagnosis.

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Myocarditis is another possible differential diagnosis that could cause chest pain, ECG changes and a raised serum troponin. Aetiology may be divided into infectious and non-infectious causes. In myocarditis, both complete recovery of left ventricular (LV) function and progression to LV dysfunction have been described. As a result, dilated cardiomyopathy (DCM) may occur from chronic inflammatory activation due to an inadequate immune response.

In this case, given all the previously described echocardiographic and CMR findings, along with the fact that the patient had no recent history of any febrile illnesses, no features of autoimmune diseases, and was not taking any drugs that could cause hypersensitivity reactions, the diagnosis was more suggestive of cardiac amyloidosis. Moreover, on the Nuclear Medicine Cardiac Amyloid scan, the mean heart to contralateral ratio (H/CL) was 1.08, thus the patient's acute presentation makes the sub-type of AL amyloidosis more likely than ATTR.

OUTCOME

The patient was discharged from the hospital, with regular follow ups by cardiology.

DISCUSSION

Cardiac amyloidosis (CA) is an infiltrative process that is characterized by bi-ventricular wall thickening with impaired relaxation and stiffening of the heart that is clinically classified as a restrictive cardiomyopathy. (Guan, *et al,* 2012).

There are three subtypes of cardiac amyloidosis. The more common type is due to immunoglobulin light chains (AL type) secreted by clonal plasma cells. The other subtypes are caused by the infiltration of a protein produced and secreted by the liver known as transthyretin (ATTR). There are 2 sub-types of ATTR, the mutant form, ATTRm and the wild type, ATTRwt.

Light chain (AL) and (ATTR) amyloidosis have a similar effect on myocardial function. However, AL is associated with more rapid development of cardiac disease and worse survival (Quarta, *et al.,* 2014). The longevity of patients with amyloidosis is directly related to cardiac involvement. Prognostic staging scores have been developed to permit prognostic evaluation, and possibly aid in the selection of treatment. A revised prognostic staging system that used N- terminal pro-hormone of brain natriuretic peptide (NT- proBNP), troponin T (cTnT) and also included the

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serum free light chain difference, reflecting the degree of plasma cell burden, was developed at Mayo Clinic and published by Kumar, *et al.* in (2012). NT-proBNP levels increase in left ventricular dysfunction, even if this is asymptomatic, whilst the troponin T rises in cardiac muscle injury (Kumar, *et al.,* 2012). This staging system was further validated in 2018, this time using the high sensitivity Troponin T. (Kumar, *et al.,* 2018).

A new staging system was recently proposed for ATTR amyloidosis, applicable to both sub-types, and this is based on NT-proBNP and eGFR (Gillmore, *et al.,* 2018).

Previously, the gold standard to diagnose cardiac amyloidosis was endo-myocardial biopsy. However, nowadays, with advances in technology and in imaging, CMR (Austin, *et al.,* 2009), echocardiography with strain, and technetium- 99m- pyrophosphate [(99m) Tc- PYP] scintigraphy (Bokhari, *et al.* 2013), can be used with confidence to confirm the diagnosis of cardiac amyloidosis in the absence of a cardiac biopsy.

Echocardiography is the best screening tool for cardiac amyloid as it is non-invasive and it may differentiate amyloidosis from other causes of left ventricular hypertrophy, as it measures the degree of diastolic dysfunction as well as the ejection fraction (EF) to global longitudinal strain (GLS) ratio for differentiating thickened hearts (EFSR**)** (Phelan, *et al.,* 2012; Liu, *et al.,* 2013). This index has been successfully used in distinguishing cardiac amyloid from hypertrophic cardiomyopathy (HCM) (Pagourelias, *et al.* 2016).

CONCLUSION

- The differential diagnosis of ventricular wall thickening include: Hypertrophic Cardiomyopathy, Metabolic Storage disorders such as Fabry's disease, Cardiac Amyloid, Myeloproliferative disorders and acute settings of myocarditis (in which case the ventricular wall thickening is due to oedema).

- The gold standard for confirming cardiac amyloidosis is endomyocardial biopsy. However, improved cardiac imaging: CMR and echocardiography with strain patterns has led to diagnosing cardiac amyloid with confidence, even without biopsy.

- There are three main types of Cardiac amyloid infiltration: Amyloid AL that is due to immunoglobulin light chains (AL) secreted by clonal plasma cells, and Amyloid ATTR that is caused by the infiltration of a protein produced and secreted by the liver known as transthyretin, and of which there are 2 subtypes, ATTRwt and ATTRm.

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- Light chain (AL) and (ATTR) amyloidosis have a similar effect on myocardial function; however when compared to ATTR amyloidosis, patients with AL have a more rapid development of cardiac disease, and worse survival.

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FIGURES

Figure 1 *– ECG of the patient, showing nSTEMI, with ST Depression/T-Wave Inversion in V5-V6, and poor R-Wave progression.*

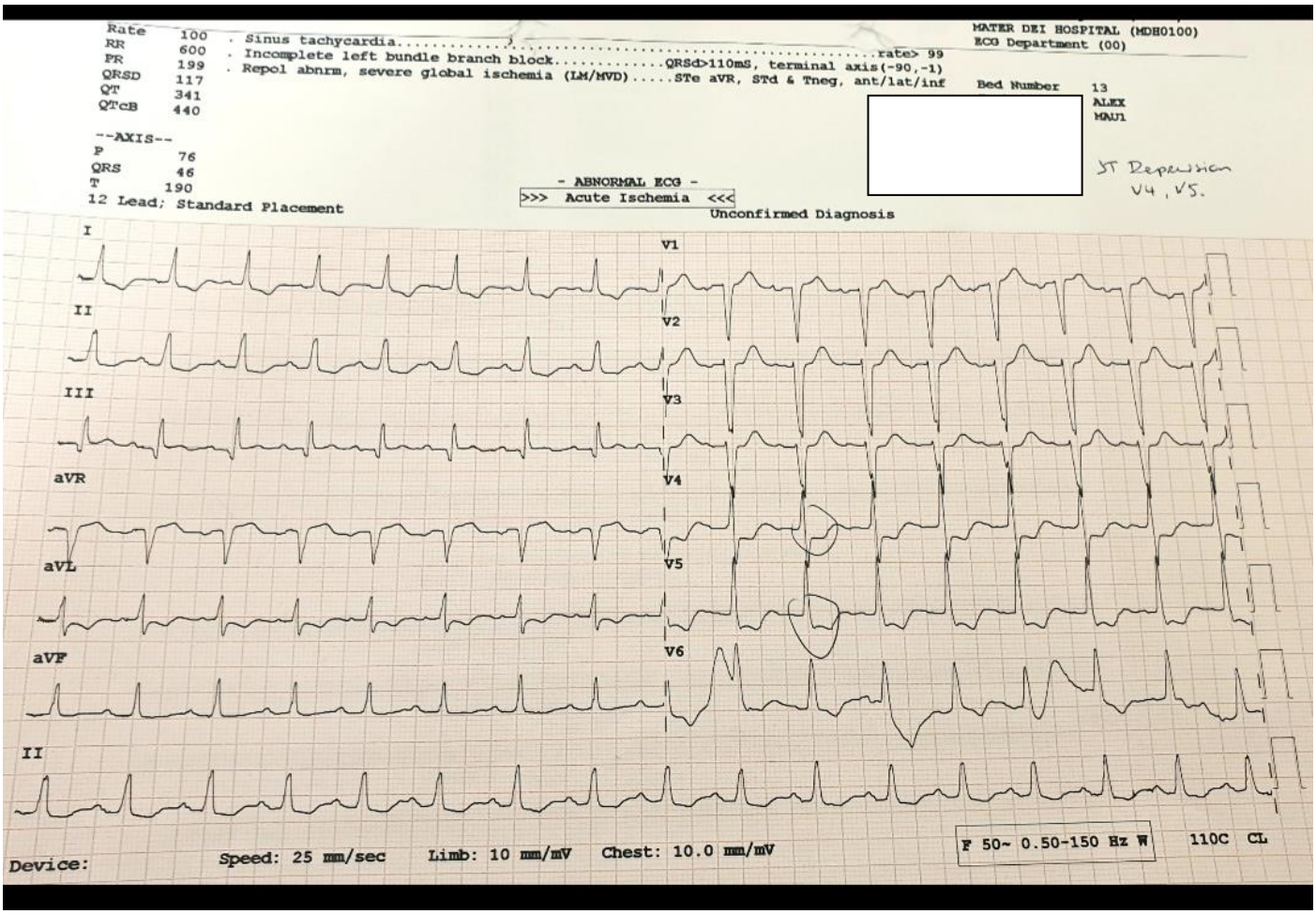

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Figure 2 – *Cardiac MRI of the patient revealing eccentric left ventricular hypertrophy, mildly impaired left ventricular ejection fraction, and severe hypo-kinesia of the basal to mid-ventricular inferior/infero-septal left ventricular walls.*

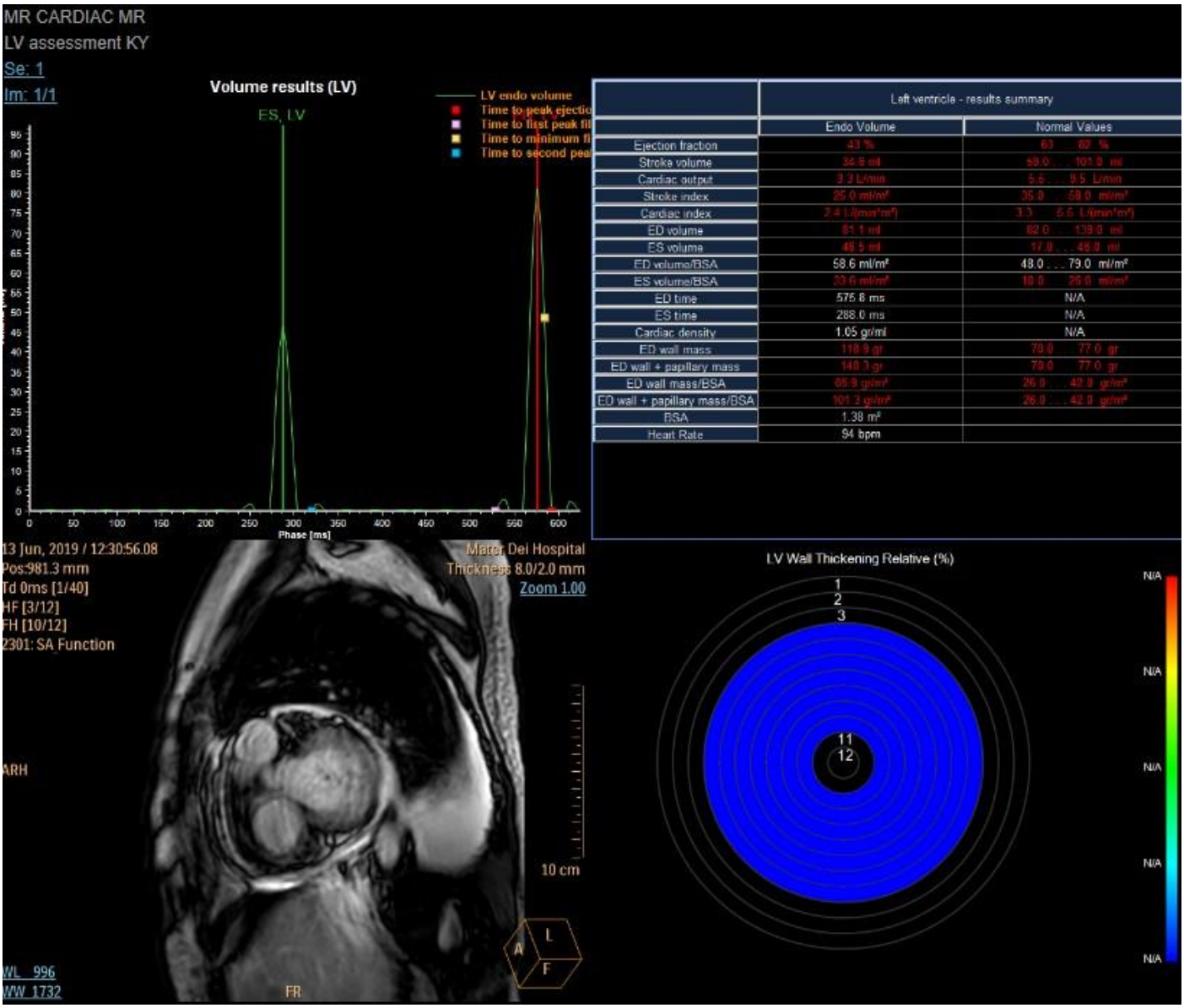

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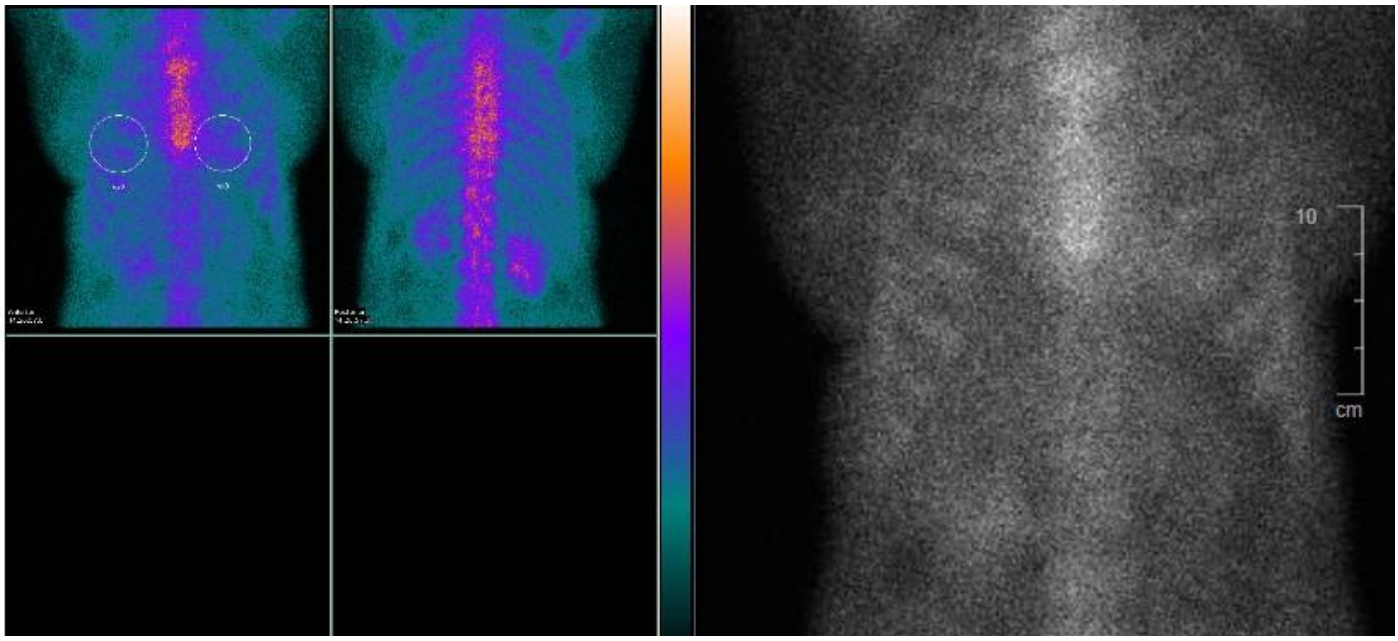
Figure 3 *– Nuclear Medicine Cardiac Amyloid Scan of the patient showing a minimally increased tracer uptake in the myocardium.*



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