

## CASE REPORT

# Cardiac Amyloid - A Hidden Contributor to Cardiac Dysfunction Following Cardiac Surgery: Case Report and Literature Review

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**Abstract:** We present two patients who underwent cardiac surgery followed by post-operative low cardiac output, diastolic dysfunction and resistance to inotropic support. Despite aggressive medical management, both patients died. At autopsy, the hearts were enlarged and showed previously undiagnosed myocardial and vascular amyloidosis. Occult cardiac amyloidosis is an uncommon, often occult, contributor to post-operative complications post cardiac surgery. Pre-operative or intra-operative myocardial biopsy may be useful in patients with unexplained diastolic dysfunction.

**Brief Summary:** We present two patients who underwent cardiac surgery followed by low cardiac output, diastolic dysfunction and resistance to inotropic support. Cardiac dysfunction was due to occult amyloidosis. Pre-operative or intra-operative myocardial biopsy may be useful in patients with unexplained diastolic dysfunction. With recent therapy advances, classification and possible treatment of amyloid are possible.

**Keywords:** Amyloid, cardiomyopathy, pathology, myocardial, surgery, complications.

## 1. INTRODUCTION

Amyloidosis is a generic term encompassing a large group of diseases characterized by the extracellular deposition of insoluble fibrillar proteins composed of  $\beta$ -pleated sheets. Amyloid is classified as primary, secondary, hereditary and age-related, with cardiac involvement occurring most commonly in primary and age-related types. The clinical symptoms of cardiac amyloidosis are generally non-specific but may present as cardiomyopathy, heart failure, coronary heart disease, valvular heart disease or arrhythmia. Conduction abnormalities, heart failure and myocardial infarctions are the main causes of death in patients with cardiac amyloidosis [1], but amyloid has seldom been reported as a cause or contributor to post-operative morbidity and mortality post cardiac surgery. We present two patients who underwent cardiac surgery whose post-operative courses were complicated by poor cardiac output and eventual death. Autopsies demonstrated extensive cardiac involvement by previously undiagnosed amyloidosis.

## 2. CASE 1

A 52-year old male ex-smoker was admitted with a non-ST elevation myocardial infarction. Past medical history was significant for hyperlipidemia, obstructive sleep apnea, and a

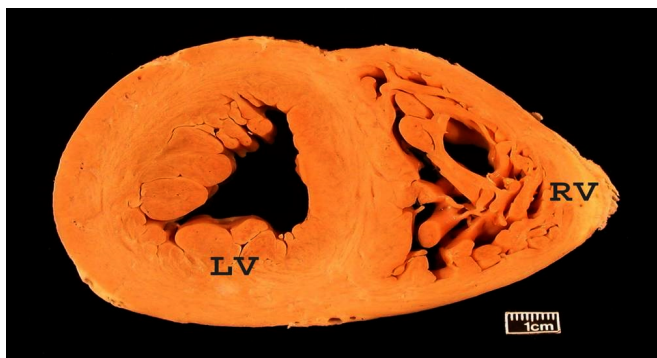
prior myocardial infarction treated with a coronary artery stent. Angiography demonstrated that the stent had undergone re-stenosis and triple coronary artery bypass grafting was undertaken. Pre-operatively the patient had severe cardiomegaly by echocardiography with moderate left ventricle dysfunction (normal systolic function with elevated left ventricle end diastolic pressure). The left ventricular ejection fraction was 57%. Myocarditis or an infiltrative process was queried. Serum electrophoresis demonstrated free lambda light chains less than 1 gram/litre. Despite these investigations, the ventricular dysfunction and cardiomegaly were attributed to ischemic heart disease. Post-operatively, he had low cardiac output requiring numerous inotropes and an intra-aortic balloon pump. Echocardiography showed diastolic dysfunction with severe thickening of both ventricles and bilateral atrial enlargement. Tamponade was not identified. Further complications developed, including atrial fibrillation requiring cardioversion, sepsis and hepato-renal failure. He continued to deteriorate and died twenty-six days after surgery.

At autopsy, heart weight was 575 g with moderate biventricular hypertrophy (Fig. 1A). All coronary artery bypass grafts were intact, patent and uncomplicated with patent distal anastomoses and distal vessels. Microscopic examination, including Congo Red stain, revealed extensive myocardial involvement by amyloid with associated micro-infarcts, chronic myocytolysis (myocyte degenerative changes), and myocyte atrophy (Fig. 1B). Amyloid was also present within the walls of small epicardial arterial branches and arterioles, as well as within the media of the vein grafts. There was no

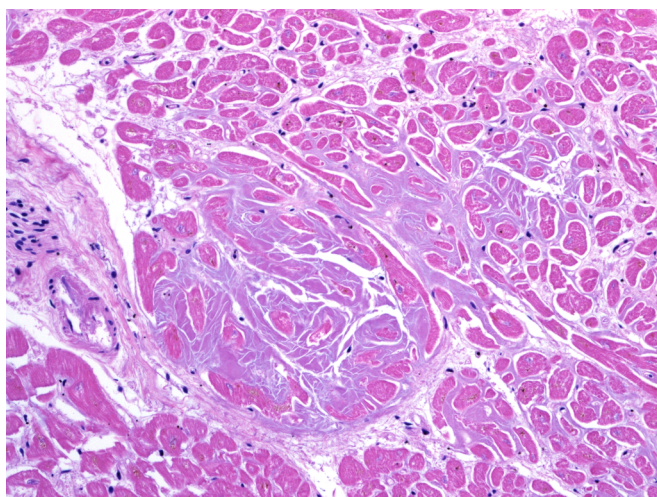
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evidence of peri-operative myocardial infarction. Systemic amyloid also moderately involved the kidneys. The amyloid was immunotyped to be of the AL type, related to the bone marrow plasma cell dyscrasia.



**Fig. (1A).** Photograph of the heart in cross section showing both right (RV) and left (LV) ventricles with mild to moderate hypertrophy. Despite being involved by severe amyloidosis the cut appearance is not that abnormal. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (1B).** Photomicrograph of the left ventricle myocardium demonstrating severe interstitial amyloid deposition between the cardiac myocytes. (Hematoxylin Eosin, H&E x 200). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### 3. CASE 2

An 86 year old man was admitted to the hospital for aortic valve replacement and coronary artery bypass grafting. His history was significant for non-insulin dependent diabetes, cerebrovascular disease, pulmonary hypertension, aortic stenosis and coronary artery disease. Cardiac catheterization was performed and there was moderate LV dysfunction but ejection fraction could not be measured due to the markedly stenotic aortic valve. Pre-operatively echocardiography demonstrated left ventricular hypertrophy and moderate left ventricular dysfunction (with normal systolic function). These were attributed to coronary artery disease and the aortic valve stenosis. No hematological abnormalities were

noted. His post-operative course was complicated by right ventricular failure, sinus tachycardia and left ventricular dysfunction requiring prolonged administration of inotropes. He developed large bilateral pleural effusions, iatrogenic pneumothorax, renal failure, digoxin toxicity and a mediastinal soft tissue abscess. He died about a month post-operatively.

At autopsy, the heart weight was 550 g with fibrous pericardial adhesions. The aortic valve prosthesis was well seated and uncomplicated. His coronary artery bypass grafts were patent, as were the anastomoses and distal vessels. Mediastinal soft tissue abscess cultures grew *Streptococcus*. Microscopic examination showed moderate to severe myocardial amyloidosis involving all chambers. The amyloid also involved the visceral vessels, the pulmonary arteries and veins. Peri-operative infarcts were absent. There was no bone marrow plasma cell disorder present. The amyloid was considered age-related in etiology in view of the patient's age and absence of a marrow disorder.

### 4. DISCUSSION

Cardiac amyloidosis is a great mimicker of many cardiac disorders and thus presents a diagnostic challenge to clinicians. In the current patients, cardiac amyloid was not clinically considered before the operations as the cardiac diastolic dysfunction and hypertrophy were attributed to coronary artery disease and valvular heart disease. Clinical signs and symptoms of cardiac amyloidosis are usually observed late in the course of the disease [2]. These include diastolic dysfunction, cardiomegaly, arrhythmias and resistance to cardio-supportive treatment. Amyloid can lead to conduction disturbances, heart failure and/or myocardial infarction [1]. The signs and symptoms are non-specific and consequently, a clinical diagnosis of cardiac amyloidosis requires a high degree of suspicion. ECG findings of cardiac amyloidosis may be helpful and include low voltage QRS complex and ST segment elevation in leads V1-V4 (pseudo-infarct pattern). In one series, these patterns were observed in 64 % and 83 % of patients, respectively [3]. There were no pre-operative characteristic ECG features in the current patients.

The hallmark of CA on echocardiogram is increased left ventricular thickness. Cardiac involvement in amyloidosis often presents with >12 mm thickness of the left ventricular wall. Increased ventricular wall thickness, left atrial enlargement, and preserved or reduced systolic function are other findings that might be present with Cardiac Amyloidosis and may be correlated with clinical congestive heart failure. Another 'classical' echocardiographic feature of cardiac amyloidosis is the 'speckled' pattern better characterized in fundamental imaging, which is a result of the amyloid protein that is more echogenic than the surrounding myocardial tissue [4].

Although signs of restrictive cardiomyopathy raise the possibility of cardiac amyloid on echocardiography and CT, cardiac MRI is increasingly utilized in myocardial evaluation. On MRI, cardiac amyloid often manifests as concentric biventricular myocardial hypertrophy with dilated atria and non-dilated ventricles, thickening of the intra-atrial septum, and diffuse subendocardial delayed enhancement in a non-vascular distribution [5]. Another challenge in the diagnosis of cardiac amyloidosis is differentiating AL from ATTR

amyloidosis by non-invasive imaging. Tc99m-PYP SPECT nuclear imaging has been proven to be a very sensitive and specific method for detecting ATTR amyloidosis, but not AL amyloidosis. Evidence of radiotracer uptake and increase in counts within myocardium can be diagnostic of ATTR cardiac amyloid. Thus, it may be useful in distinguishing the two types of cardiac amyloidosis [4].

At autopsy, hearts infiltrated by amyloid are typically firm, rubbery, and non-compliant. These macroscopic features can mimic hypertrophic cardiomyopathy (*i.e.* thickened walls without dilation), although microscopy differentiates the disorders. By light microscopy, cardiac amyloid deposits show extracellular deposition of pale, eosinophilic, and amorphous material on H&E (hematoxylin and eosin) staining, and apple green birefringence with polarization on Congo Red stain.

Occult cardiac amyloidosis has only rarely been described as contributing to mortality or morbidity in post-operative cardiac surgery patients [6]. The most common causes of peri-operative death following cardiac surgery include myocardial infarction, congestive heart failure, ventricular arrhythmias and stent thrombosis in those patients who had prior coronary stenting [7]. Non-cardiac causes of death include infection, stroke, and respiratory failure [7].

A variety of surgical and anaesthetic factors may contribute to mortality in patients with cardiac amyloidosis. The stresses produced by fluid replacement and hemodynamic changes may trigger myocardial ischemia in a heart compromised by amyloid deposition [1]. Amyloid may cause ischemia due to small vessel and epicardial vessel involvement. Amyloid may cause myocardial diastolic dysfunction and heart failure. Arrhythmias may be poorly tolerated. Atrial fibrillation may result in loss of ventricular filling. Amyloid may also be arrhythmogenic due to ischemia.

Prominent diastolic dysfunction noted pre-operative or intra-operatively should lead to consideration of myocardial biopsy which is easily accomplished. Knowledge derived from such a biopsy may prove useful for the management of the patient. More than 25 different proteins are known to cause amyloidosis. Clinically, the most important amyloidogenic proteins are serum amyloid A (SAA), transthyretin (TTR), and immunoglobulin kappa (IGK) or lambda light chains (IGL; so-called primary or AL type). They account for more than 90% of systemic amyloidosis. The management of amyloidosis relies on the treatment of the underlying etiology, often by high-risk, aggressive modalities such as high-dose chemotherapy and stem cell transplantation or liver transplantation. Specific medical therapies are evolving. Hence the accurate subtyping of amyloid deposits in clinical biopsy specimens is of paramount importance [8].

Amyloid typing is typically conducted *via* immunohistochemistry (IHC) and immunofluorescence (IF) analysis of formalin-fixed paraffin-embedded (FFPE) and/or the native frozen fixed tissue samples. However, IHC often yields inconclusive results, because the antigenic epitope may be lost during FFPE tissue preparation and contamination of samples by serum proteins can result in high background staining [9, 10].

Laser microdissection (LMD) followed by liquid chromatography (LC) combined with mass spectrometry (LMD-LC-MS) is the typical advanced proteomic approach for the correct diagnosis and typing of amyloidosis. LMD-LC-MS enables determination of complete protein composition and identification of the most abundant amyloid proteins from a minimal number of tissue samples [9].

Transthyretin amyloidosis cardiomyopathy (ATTR-CM) is an increasingly recognized cause of heart failure in older individuals. ATTR is due to misfolding of the liver-derived precursor protein transthyretin (TTR) (previously called pre-albumin), either as an acquired wild-type variant (ATTRwt) or as a hereditary mutant variant (ATTRh). The ATTRm variant, caused by one of many different point mutations in the TTR gene, can manifest as a polyneuropathy, cardiomyopathy, or a mixed phenotype that varies according to the specific mutation. Hereditary and acquired cardiac transthyretin amyloidosis are associated with markedly poor quality of life at the time of diagnosis [10].

ATTR-CM progresses to death within a few years, and till recently has not been treatable. However, several very promising new therapies are now in development. Two gene-silencing therapies reduce circulating transthyretin (TTR), and halt or slow the progression of ATTRh polyneuropathy: inotersen, an antisense oligonucleotide and patisiran, a small interfering RNA. These treatments may have favorable cardiac effects in Hereditary Transthyretin Cardiac Amyloidosis (ATTRh-CA) and Wild type Transthyretin Cardiac Amyloidosis (ATTRwt-CA) as well [11].

There are other treatments that stabilize the TTR tetrameric structure preventing tetramer dissociation, which is the rate-limiting step in TTR amyloid fibril formation. Tafamidis is a small molecule engineered to bind to the thyroxine binding pocket of TTR and stabilizes the TTR tetramer. The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial demonstrated that tafamidis reduced mortality and cardiovascular hospitalizations in both ATTRwt-CA and ATTRh-CA along with a slowing of the decline in functional capacity and quality of life. These therapies work by inhibiting amyloid fibril formation and may be more efficacious if administered earlier in the course of the disease when there is less cardiac dysfunction from amyloid deposits [11-13].

This report reinforces the value of autopsy in determining the pathoetiology of mortality and morbidity in cardiac surgery patients. New information that would have changed clinical management is detected in 5-19 % of post mortems from patients with recent cardiac surgery [14]. Without an autopsy, the cause of low cardiac output may have been erroneously attributed to ischemic heart disease or another cause of ventricular dysfunction.

Investigation and treatment of underlying bone marrow disorders or new therapies for transthyretin related cardiomyopathy may be appropriate in some patients. Finally, the utilization of a percutaneous or trans-catheter valve approach may be a better choice for patients with significant valve disease.

## CONCLUSION

Occult cardiac amyloidosis can contribute to post-operative morbidity and mortality. There are often no specific pre-operative or post-operative clinical signs or symptoms. Cardiac surgery can complicate the clinical picture as many of the observed signs and symptoms can be attributed to post-operative complications including arrhythmias, tamponade and ischemia. Amyloid may contribute to peri-operative diastolic dysfunction and may be diagnosed with a pre-operative or intra-operative myocardial biopsy. The results may be useful in clinical management, including palliation, treatment of the disorder causing the amyloid or in the choice of an alternative therapeutic approach such as percutaneous or trans-catheter valve replacement.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## STANDARD OF REPORTING

CARE guidelines and methodology were followed in this study.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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