

## Intraoperative death due to nodular amyloidosis cardiomyopathy associated with fat pulmonary embolism

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**Abstract:** Cardiac amyloidosis is caused by extracellular deposits containing low molecular weight protein subunits arranged in a beta sheet configuration. By gross examination amyloid deposits are identifiable as localized tan, waxy appearing lesions affecting almost always the atria (usually atrial endocardium), valve leaflets, ventricular, but also in the coronary lumen, sometimes leading to severe coronary stenosis. Fat pulmonary embolism is a known complication of femoral fractures, being more frequent in untreated cases compared to those suffering surgical interventions. We present a case in which a female patient with cardiac amyloidosis died on the operating table, the direct cause of death being fat pulmonary emboli, and discuss the involvement of the associated cardiac amyloidosis in thanatogenesis.

**Key Words:** cardiac amyloidosis, fat embolism, intraoperative death, femoral fracture.

Cardiac amyloidosis (amyloid cardiomyopathy, AC) is caused by extracellular deposits containing low molecular weight protein subunits arranged in a beta sheet configuration, leading to restrictive cardiomyopathy [1] and electrical conduction disturbances [2, 3].

AC may mimic constrictive pericarditis, coronary artery disease, valve heart disease, and idiopathic hypertrophic or congestive cardiomyopathy [4].

By gross examination amyloid deposits are identifiable as localized tan, waxy appearing lesions affecting almost always the atria (usually atrial endocardium), valve leaflets, ventricular walls (often

associated with fibrous replacement lesions), but also the coronary lumen, sometimes leading to severe coronary stenosis (>75%) [5].

Cardiac amyloidosis is almost always associated with amyloid deposits located in other organs [5]. The extent of amyloid deposition can be graded from 1 to 4 (less than 10%, 10 to 25%, 26 to 50%, and more than 50% involvement of the myocardium, respectively) and the pattern of deposits can be classified as nodular, perifibrillar, or mixed, with or without vascular involvement [6]. Genetically AC can be primary light chains amyloidosis (AL) or familial transthyretin-related (ATTR) amyloidosis. The AL amyloidosis is caused by

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the deposition of immunoglobulin light chains (kappa or lambda), performed by monoclonal gammopathy. ATTR amyloidosis is an autosomal dominant disorder caused by the amyloidogenic form of transthyretin, a plasma protein synthesized in liver [7, 8].

Other types of amyloidosis with possible cardiac involvement are: senile systemic amyloidosis caused by the wild-type transthyretin, secondary amyloidosis after chronic systemic inflammation, and beta (2)-microglobulin amyloidosis after long-term dialysis treatment [8]. If ATTR amyloidosis may be indolent, untreated AL amyloidosis with clinical cardiac involvement is a rapidly fatal disease. The management decisions of cardiac amyloidosis are based on the underlying cause. Although treatment of senile systemic amyloidosis is largely supportive, the therapeutic approaches for AL amyloidosis include chemotherapy, autologous stem cell transplantation, and, rarely, cardiac transplantation [9]. The main causes of death in amyloid cardiomyopathy are restrictive cardiac insufficiency and cardiac conduction disturbances, but thromboembolic disease or acute myocardial infarction are potential causes as well [10-13].

As AC is usually identifiable in older ages, and is often associated with a longer evolution, it is rarely a considered a cause of sudden death. In monitored patients with cardiac amyloidosis whose death was sudden (circumstance in which, even if the death is sudden, it circumvents the definition of sudden cardiac death), the most likely immediate cause of death was electromechanical dissociation; ventricular fibrillation appears in patients with a less severe heart failure [14]. We present a case in which a patient with cardiac amyloidosis died on the operating table, the direct cause of death a trochanteric fracture causing fat pulmonary emboli, and discuss the involvement of AC in thanatogenesis.

## CASE REPORT

### *Clinical data.*

An 84 years old female patient, with a left pertrochanteric fracture was admitted in the Orthopedics department. Personal history revealed coronary heart disease, essential hypertension, congestive heart failure class II NYHA, mitral regurgitation, aortic disease, tricuspid regurgitation, secondary pulmonary hypertension, chronic atrial fibrillation, obesity, dyslipidemia. Lab works at admission revealed a slightly elevated Quick time (13.6 sec), decreased potassium (3.17 mmol/dL), increased fibrinogenemia (641 mg/dL). The fracture was considered a candidate for open reduction using a locked intramedullary fixation. During surgery the patient suffered a respiratory arrest, which was initially resuscitated but immediately after the patient suffered a cardiac arrest preceded by bradycardia, unresponsive to CPR measures.

## **Histopathology investigation**

### *Material and methods*

Samples of myocardial tissue from two different areas of the anterior wall of the left ventricle were taken for histopathology investigation. Specimens from brain, lungs, liver, kidney and spleen were taken as well.

The tissue samples were fixed in 10% neutral buffered formalin (pH - 7) for 24–48 hours and paraffin embedded. Sections were cut at 5 µm and stained with standard HE, elastic van Gieson and Congo Red. Scharlach stain was performed in lung samples on frozen sections.

*Immunohistochemistry* for amyloid precursor protein (APP, clone 3G12, dilution 1:50, producer Novocastra) was done on heart specimens, using sections displayed on slides treated first with poly-L-lysine. IHC was performed on 3 µm thick sections from formalin-fixed paraffin-embedded specimens, according to the indirect triserial Avidin-Biotin-Complex method of Hsu [15], modified by Bussolati and Gugliotta [16].

Briefly, the procedure comprised: deparaffination in toluene and alcohol series, rehydration, washing in phosphate buffer saline (PBS), blocking with normal serum, for 20 min, incubation with primary antibody for one hour, then with polymeric HRP-linker antibody conjugates (NovoLink Polymer Detection Systems, Novocastra), washing in PBS and developing with 3.3'-DAB.

Antigen retrieval technique (heat induced epitope retrieval for paraffin sections) was done according to the producer's specifications.

To ensure the reliability of the experimental study, internal quality control of histopathologic and IHC techniques were performed as a part of an implemented and certified quality assurance system (ISO 9001/2008).

All slides were examined and photographed on a Zeiss AxioImager microscope (Gottingen, Germany). Digital images acquired with Zeiss Axio Vision program have been processed and analyzed with ACDSee Pro Photo Manager (Washington DC), running under Windows Vista.

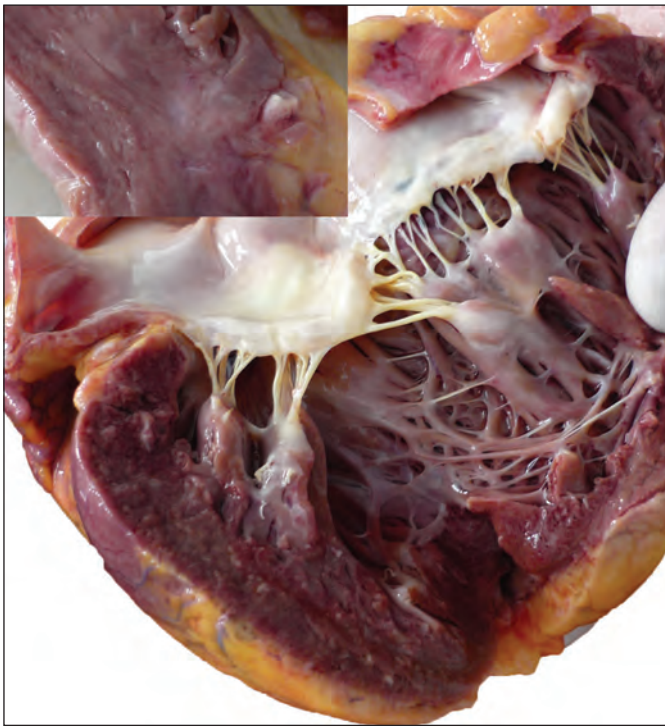
## RESULTS

Macroscopic appearance revealed an old ischemic stroke located in the left occipital area, partially collapsed lungs, a myocardium with frequent waxy, tan nodules and small fibrotic areas (Figure 1), smooth heart valves, first-second degree coronary atherosclerosis, stasis liver, kidney cysts and chronic pyelonephritis.

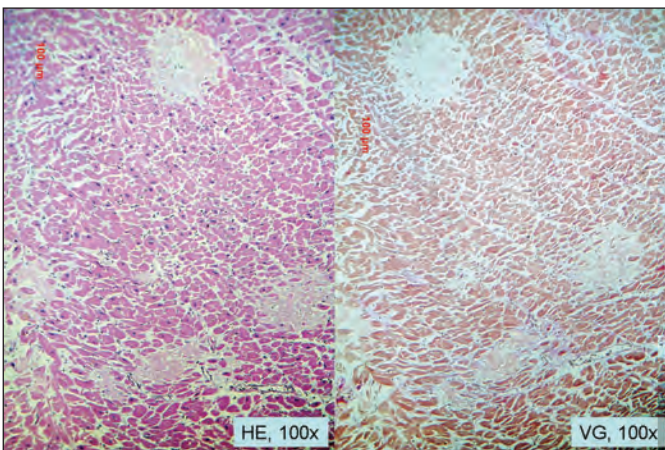
The microscopic study revealed interstitial nodular deposits of a pink amorphous material disseminated in the myocardium, not stainable with van Gieson (Figure 2).

The nodular deposits stained orthochromatically with Congo Red (Figure 3) and showed green-apple birefringence in polarized light (Figure 4). IHC for APP (amyloid precursor protein) was intense positive

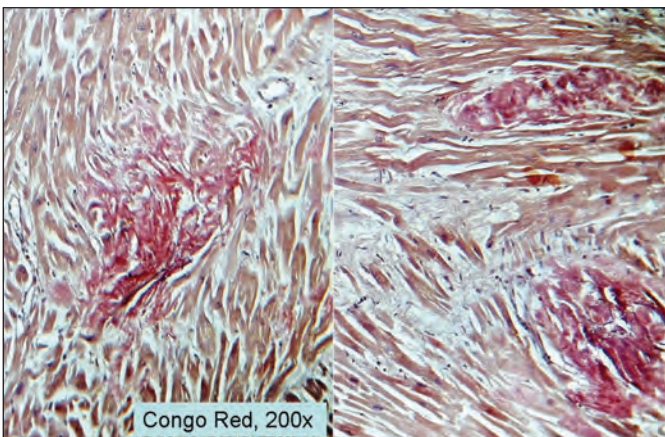




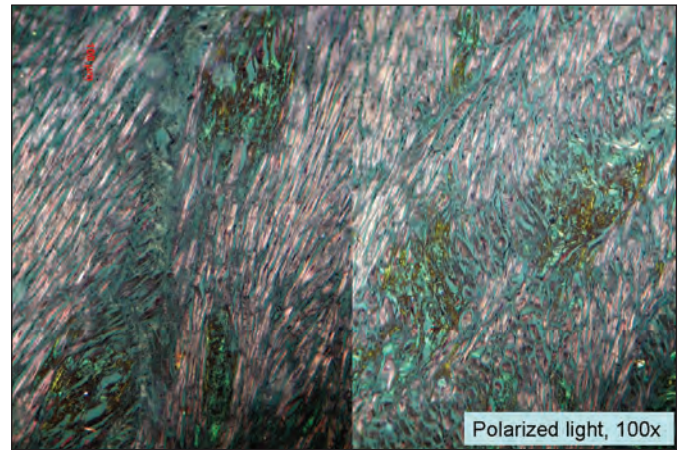
**Figure 1.** Gross appearance of cardiac amyloidosis: nodular, tan, waxy spots within the cardiac muscle. Inset - detail



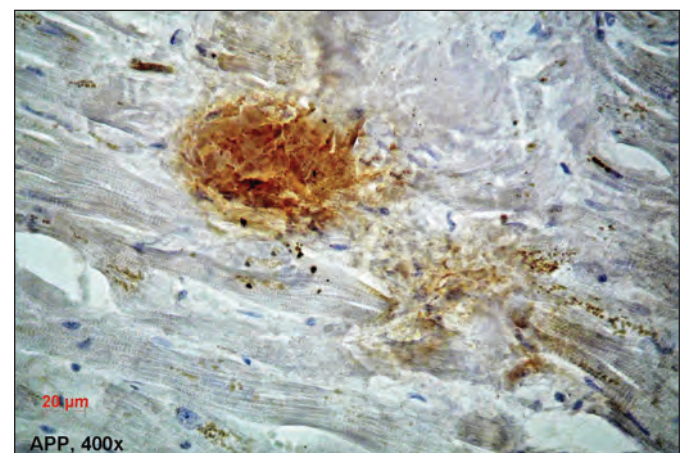
**Figure 2.** Interstitial nodular deposits of amyloid (pink amorphous material) in myocardium, HE, 100x (left), which did not stain with van Gieson, VG, 100x (right)



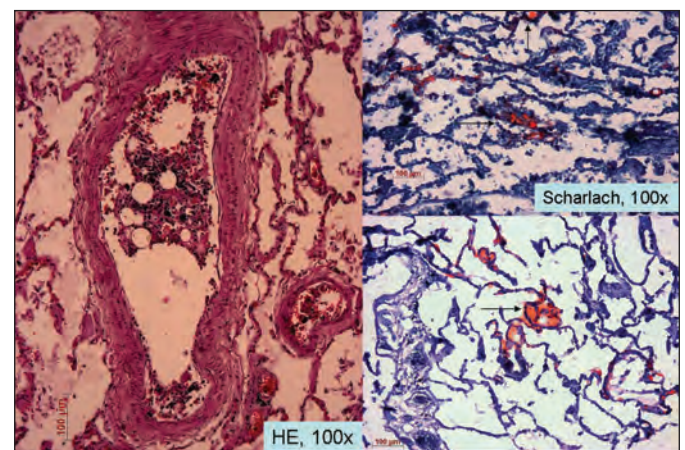
**Figure 3.** Orthochromatic stain of the amyloid deposits with Congo Red, 200x



**Figure 4.** Green-apple birefringence of the amyloid under polarized light, 200x



**Figure 5.** Intense IHC reaction for APP in nodular deposits, IHC, 400x



**Figure 6.** Pulmonary embolism with bone marrow in a medium size vessel in lung, HE, 100x (left); pulmonary embolism with lipids in capillaries in lung, Scharlach, 100x (right)

in nodular deposits (Figure 5). The extent of amyloid deposition was mild to moderate (grade 2: ~ 10% - 15% involvement of the myocardium). Small arterioles within myocardium were not affected.

Focal vascular lesions with various degrees of wall thickness due to amyloid deposition were found in lungs (not shown). Pulmonary embolism with bone marrow and lipids was also identified (Figure 5).



Other organs (brain, liver, kidney, spleen) showed no signs of amyloid involvement.

## DISCUSSIONS

In a study conducted on 11 patients with endomyocardial biopsy, various aspects of amyloidosis were noticed such as nodular deposits, thick perimyocytic layers of amyloid and small myocyte diameters, associated with small-vessel involvement and myofilament loss [17].

Intraoperative death associated with cardiac amyloidosis was previously described. For example Tallgren et al described a case associated with renal transplantation in a patient with secondary amyloidosis due to rheumatoid arthritis and another one associated with liver transplantation due to primary hepatic amyloidosis with subsequent liver failure [18]. The cause of death was heart block in the first case and bradycardia in the second. Eriksson described seven cases of familial amyloid neuropathy who developed severe bradycardia or heart block during anesthesia [19]. Even though arrhythmias are frequent in AC, bradyarrhythmias are rare [20], but are identifiable under anesthesia, the main cause being, most likely, the presence of infiltrative lesions at the level of the cardiac conduction system, leading to an increased

susceptibility to the depressant action of various anesthetic substances [19]. Another possible cause is autonomic heart dysfunction cause by amyloid neuropathy [19, 21].

Fat pulmonary embolism is a known complication of femoral fractures, being more frequent in untreated cases compared to those suffering surgical interventions [22]. Fat emboli related death in femoral surgery is usually preceded by a free period of time of minimum two days, but intraoperative death were described as well [22].

## CONCLUSIONS

The involvement of AC in thanatogenesis is disputable as initially the patients suffered a respiratory arrest. However, as it is known that anesthetics increase the risk for bradyarrhythmic events in patients with AC, and that after the resuscitated respiratory arrest the patient presented a severe bradyarrhythmia, we considered AC to be an enabling condition, which, associated with the respiratory pathology lead to non-resuscitable asystole.

Our case, associated with those presented above suggests that anesthetics should be used cautiously in patients with suspected cardiac amyloidosis. If confirmed, alternate, non-surgical methods of treatment should be used whenever possible.

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