

*Professor Ivo Šteiner, MD, PhD, Editor*

## CASE 2-2011: CARDIAC AMYLOIDOSIS

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### Introduction

Amyloidosis is characterized by accumulation of extracellular fibrillar protein (amyloid) in connective tissues. The diagnosis is established by demonstration of the typical birefringent tissue deposits seen with Congo red staining. Five basic types of amyloidosis have been described according to the underlying disease (5):

1. Immunoglobulin (AL) amyloidosis, or primary amyloidosis
2. Familial amyloidosis
3. Senile systemic amyloidosis
4. Secondary (AA) amyloidosis
5. Hemodialysis-associated amyloidosis.

Clinically apparent heart disease is present in one-third of patients (15), although the heart is virtually always involved when studied pathologically (14). Involvement of the heart is a common finding and a very frequent cause of death (4). Cardiac amyloidosis usually occurs during primary (AL) amyloidosis, familial amyloidosis (with peripheral neuropathy, renal impairment and gastrointestinal symptoms) (2, 9), and senile systemic amyloidosis (7, 10, 11, 12). Primary amyloidosis is often seen in people with multiple myeloma cancer. Cardiac amyloidosis („stiff heart syndrome“) occurs when amyloid deposits take the place of normal heart muscle. Amyloid containing myocardium becomes firm, rubbery, and noncompliant (6). It is the most typical type of restrictive cardiomyopathy. A second common presentation is congestive heart failure related to systolic dysfunction, which is usually a late finding in cardiac amyloidosis (3). Haemodynamic evidence of restriction of ventricular filling may not be prominent in these patients. Orthostatic hypotension occurs in about 10 percent of cases. Although it is most likely due to amyloid infiltration of the autonomic nervous system or blood vessels, or both, amyloid deposition in the heart and adrenal glands may contribute to the pathogenesis of this variant (8). Cardiac amyloidosis may affect the way electrical signals move through the heart (conduction system). This can lead to arrhythmias and conduction disturbances (heart block). Sudden death, presu-

mably arrhythmic in origin, is relatively common and may be preceded by episodes of syncope (1, 13). Secondary amyloidosis (AA type) rarely affects the heart. Cardiac amyloidosis is more common in men than in women. The disease is rare in people under the age of 40.

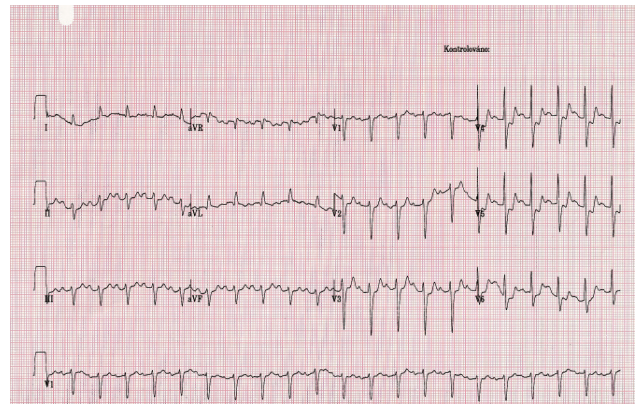


Fig. 1: ECG on admission.

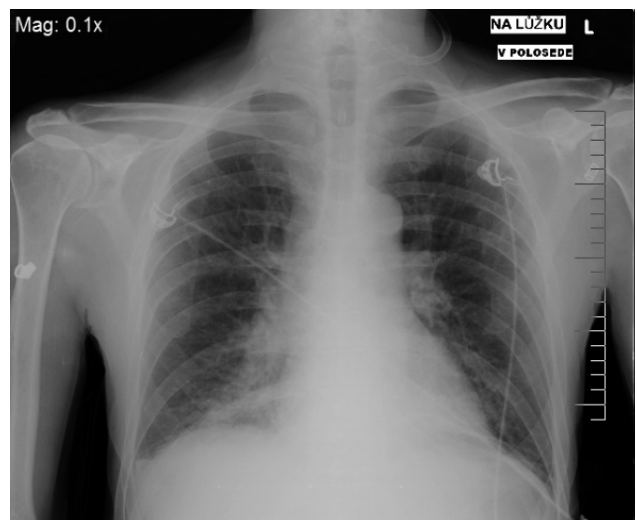
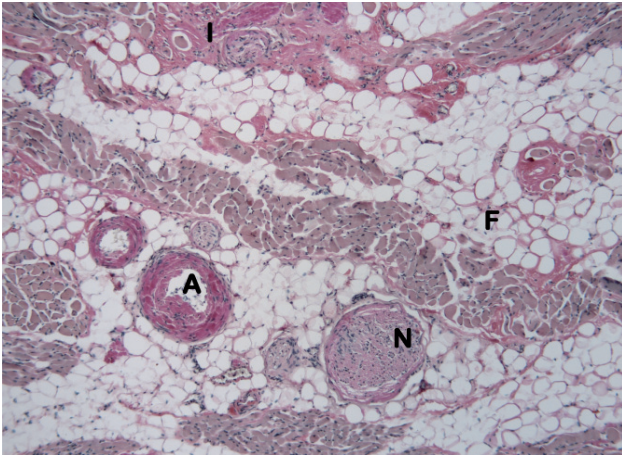
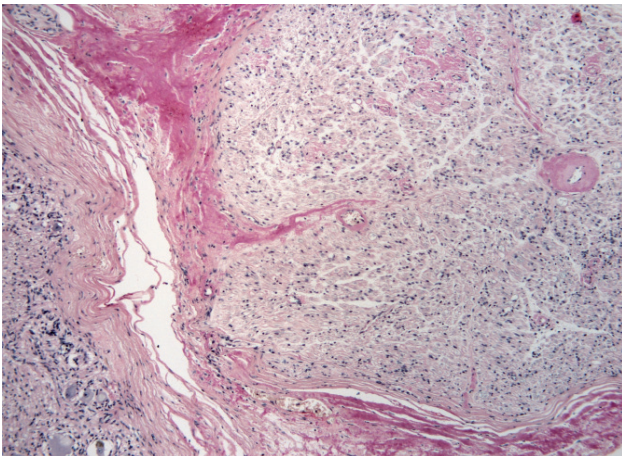


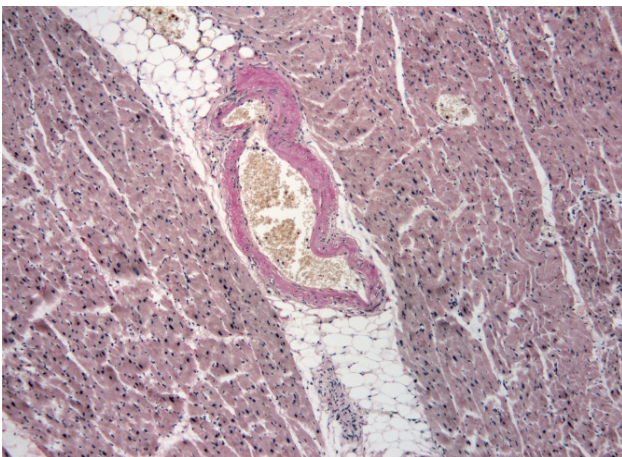
Fig 2: Chest X-ray with nearly normal findings.



**Fig. 3:** Amyloid involvement of the tongue. Presence of amyloid in the: A - small artery; N - nerve; F - adipocytes basal membranes; I - interstitium. (Sirius red staining).



**Fig. 4:** Spinal nerve. Amyloid depositions in the perineurium, focally in the endoneurium and in the wall of the small vessels. (Sirius red staining).



**Fig. 5:** Presence of amyloid in the wall of an intramyocardial artery. (Sirius red staining).

## Clinical data

A 59-year-old man was admitted to Intensive care unit of our clinic for respiratory failure. He had history of idiopathic chronic polyneuropathy with axonal involvement of sensitive and motor fibres of peripheral nerves on the upper and lower extremities. This diagnosis was based on results of clinical examinations and electromyography. Other paraclinical examinations were negative and the therapeutical test with glucocorticoids was without any effect. This patient was completely immobile due to this neurological involvement during the last several months. He was also treated for rheumatoid arthritis and osteoporosis in last 3 years.

There was history of productive cough with white sputum expectoration few days before admission and rapid breathlessness progression without fever about 6 hours before admission. For suspicion of pulmonary oedema he was sent to hospitalisation. He was dyspnoeic in rest with hypotension and bradycardia with rapid progression to unconsciousness on admission. Artificial ventilation was promptly started with cardiopulmonary resuscitation.

Results of laboratory examinations were inaccessible during the time of admission. The ECG showed sinus tachycardia with diffuse non specific ST segment denivelations (Fig. 1), with no evidence of acute coronary syndrome. The chest X-ray demonstrated nearly normal findings (Fig. 2). In harmony with physical examination findings, we suggested that heart failure is not the cause of the patient's problems. The screening echocardiography during resuscitation showed right ventricle dilatation as a sign of possible severe pulmonary embolism. Therefore the diagnosis of pulmonary embolism was suggested and thrombolysis was administrated. The other finding was severe left ventricle dysfunction. However all these arrangements were without any effect and the patient died 1 hour after admission due to progressive shock.

## Pathology

The gross findings were insignificant - generalized muscle atrophy (180 cm/53 kg), pulmonary congestion and edema, acute bronchitis with focal bronchopneumonia, mild left ventricular hypertrophy (heart wt. 380 g), and right ventricular dilatation. There was an interesting finding of mild macroglossia.

It was only histology, which established the final diagnosis. The H&E stain, confirmed by special stains (Sirius red, Congo red), showed deposits of amyloid in multiple organs and tissues (kidneys, myocardium, adipose tissue, skeletal muscles, lungs, bowels, etc.) particularly in their small vessels. In the tongue, there was, in addition to the small vessel involvement, deposition of amyloid also in the interstitium. Extensive examination of the nervous system (CNS, spinal cord, peripheral nerves) revealed involvement of the latter only; there were amyloid deposits in the small vessels and also markedly in the perineurium and focally in the endoneurium.

Immunohistochemical typing of the amyloid showed light chain (AL) amyloidosis lambda. The presence of light



chains lambda in proximal renal tubules is suspicious of monoclonal gammopathy.

## Discussion

Amyloidosis is a complex disease which can involve many organs and cause organ dysfunction. As cardiac involvement worsens the prognosis and may influence treatment strategies, all patients with known amyloidosis should be screened for cardiac amyloidosis even if they have no cardiac symptoms. Cardiac involvement should be suspected in patients with systemic amyloidosis who develop congestive heart failure and/or conduction system abnormalities in the absence of notable coronary artery disease. Restrictive cardiomyopathy and prominent signs and symptoms of right-sided heart failure should raise the suspicion of cardiac amyloidosis. Endomyocardial biopsy is the best diagnostic tool, although a combination of characteristic ECG and echocardiographic findings and a positive extracardiac tissue biopsy may provide an alternative approach. The overall prognosis of cardiac amyloidosis is poor; however, recent advances in treatment, including chemotherapy, autologous stem-cell transplantation, and combined heart and liver transplantation, have offered increased survival and improvement in organ function. Anticipated advances and insights in molecular biology, genomes, imaging techniques, biochemical markers, and quantitative detection of amyloid proteins, along with new treatment strategies, offer hope for the future (5).

## Message from Editor (prof. Šteiner)

The patient's illness presented itself as a neurological disorder – polyneuropathy of a mixed type (both axonal and demyelinating). There also appeared a vague diagnosis of rheumatoid arthritis (IgM) with nephropathy. However, the correct diagnosis of amyloidosis was achieved only post-mortally.

The AL amyloidosis (amyloid light chain) may occur in any dyscrasia of the B-lymphocyte lineage, such as multiple myeloma, Waldenström's macroglobulinaemia, solitary plasmacytoma, malignant lymphomas, and "benign" monoclonal gammopathies. The incidence of "benign" monoclonal gammopathies is probably around 10 %.

AL amyloid is the most common form of amyloidosis. It is commoner in men than women, and usually occurs in patients over 40 years old. It predominantly affects the mesenchymal tissues to produce clinical effects as neuropathies, carpal tunnel syndrome, macroglossia, restrictive cardiomyopathy, and arthropathies of large joints.

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The great majority of patients with AL amyloidosis do not have classic multiple myeloma or any other overt B-cell neoplasm. In virtually all such cases, monoclonal immunoglobulins or free light chains can be found in the patient's serum or urine. Clearly, these patients have an underlying B-cell dyscrasia in which production of an abnormal protein, rather than production of tumor masses, is the predominant manifestation.

In the presented case there appear two major clinical drawbacks preventing achievement of the correct diagnosis. First, it is the lack of surgical pathology examination. A simple biopsy of a peripheral nerve, or e.g. rectal mucosa or abdominal subcutaneous fat, would certainly lead to the desired goal. Second, no examination towards monoclonal gammopathy, e.g. bone marrow, serum, or urine, was performed.

To conclude, amyloidosis remains a treacherous disease and all medical specialities should keep its possibility in mind.

## Acknowledgment

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