Pathology (April 2018) **50(3)**, pp. 261–268

REVIEW

Cardiac amyloidosis: from clinical suspicion to morphological diagnosis

Pavla Flodrova[1], Patrik Flodr[1], Tomas Pika[2], Jiri Vymetal[3], Dusan Holub[4], Petr Dzubak[4], Marian Hajduch[4], Vlastimil Scudla[2]

[1]*Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic;* [2]*Department of Hemato-Oncology, University Hospital Olomouc, Olomouc, Czech Republic;* [3]*Department of Internal Medicine III – Nephrology, Rheumatology and Endocrinology, University Hospital Olomouc, Olomouc, Czech Republic;* [4]*Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc, Olomouc, Czech Republic*

Summary

Amyloidosis is a heterogeneous group of diseases characterised by extracellular accumulation of amyloid in various tissues and organs of the body, leading to alteration and destruction of tissues. Heart involvement is the most important prognostic factor in patients with systemic amyloidosis and the diagnosis and typing of amyloid must be made properly. The clinical picture shows congestive heart failure with predominant right-sided heart failure symptoms in fully developed disease, various types of arrhythmias and characteristic electrocardiography and echocardiography findings. Blood and urine monoclonal protein studies and cardiac biomarkers belong to the spectrum of standard laboratory examinations. Cardiac cardiomyopathy is connected with amyloid based on immunoglobulin light chains, serum amyloid A, transthyretin, atrial natriuretic factor or apolipoprotein A1. In the routine diagnostic algorithm, biopsy specimens are examined using special histological staining, immunohistochemistry and immunofluorescence; proteomic analysis is only performed in specialised centres.

Key words: Amyloidosis; immunoglobulin light chains; transthyretin; AL amyloid; AA amyloid; echocardiography.

Received 30 March, revised 8 August, accepted 16 October 2017
Available online 12 February 2018

INTRODUCTION

Amyloidosis is a heterogeneous group of diseases characterised by extracellular accumulation of amyloid in various tissues and organs of the body, which leads to alteration and eventually destruction of tissues with impairment of organ function or even organ failure. Amyloid is defined as an insoluble or poorly soluble complex deposit composed of a principal proteinaceous part and other substances. The proteinaceous component is subtype-specific and is formed by normally soluble monomeric proteins, which are turned into a pathological fibrillar form due to gene mutation, production of a clonal B-cell neoplastic population, inherent instability of a wild-type protein, overproduction of the normal protein with reduced stability and an increased propensity to misfold.[1] The fibrillar form, amyloid fibrils, contains a high proportion of cross-β-sheet in the secondary conformation and is stabilised by intra- and intermolecular interactions. Besides others, these properties result in resistance to proteolytic degradation. Amyloid fibrils are rigid, non-branching fibrils with a diameter of approximately 10 nm.[2] The co-precipitated molecules carry various chemical compounds, in particular proteoglycans, glycosaminoglycans and lipoproteins. The most frequent additional substances in amyloid are serum amyloid P component, apolipoprotein E, apolipoprotein A1 and apolipoprotein A4.[3–6]

According to the extent of involvement, amyloid disease may be systemic or localised; other classifications are based on heredity (acquired/inherited) or amyloidogenic proteins. The 2014 nomenclature of amyloid fibril proteins defines 31 known extracellular fibril proteins in humans.[2]

THE ROLE OF ENDOMYOCARDIAL BIOPSY IN THE DIAGNOSIS OF AMYLOIDOSIS

Endomyocardial biopsy (EMB) is an invasive diagnostic method usually performed by experienced teams in specialised medical centres to ensure a low rate of overall complications, ranging from 1% to 2%.[7] The technique of non-surgical cardiac biopsy was developed in dogs in the late 1950s using a transthoracic approach, which was superseded by the use of flexible catheter-tip biopsy forceps in the 1960s.[8]

EMB is indicated for evaluation of specific heart involvement in a narrow spectrum of cases, for example in monitoring after cardiac transplantation, in patients with suspected myocarditis, cardiomyopathy, drug toxicity or in systemic conditions where heart disease is presumed such as various storage diseases (lipidosis, glycogen storage diseases and amyloidosis).

Adequate biopsy sampling is necessary for an accurate diagnosis and multiple specimens of myocardial tissue of sufficient sizes are required, with a recommended diameter of 1–2 mm.[7] Recommendations for the number of biopsy samples can be found in the Association for European Cardiovascular Pathology guidelines.[9] Another three, or preferably four, formalin fixed tissue specimens and one or two snap-frozen or RNAlater treated tissue samples (tissue treated with RNA-preserving solution to prevent damage of RNA) should

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2017.10.012

be obtained for additional specific examinations (e.g., PCR detection of pathogens).

Moreover, proper handling is important for the most relevant results. Therefore, careful removal of tissue from the bioptome without using forceps is necessary to prevent crush artifacts and damage to the sample.

Pathologists have several possibilities for tissue examination. The essential approach is light microscopy using basic or special histological staining (Fig. 1 and 2) or immunohistochemical staining (Fig. 3) performed on formalin fixed, paraffin embedded (FFPE) samples. Non-fixed tissue samples are needed for immunofluorescent staining. The subcellular dimension of ultrathin sections may be examined with electron microscopy, which requires specific workflow and sample preparation using Karnovsky's solution or glutaraldehyde for fixation and resin for embedding.

Amyloid deposits in the heart may be suspected thanks to modern imaging methods, but EMB with morphologically confirmed amyloid is widely required for the definite diagnosis. According to the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology, EMB is the gold standard for diagnosis of storage diseases.[7] Recently, new non-invasive diagnostic approaches with good levels of sensitivity and specificity have been described; for example, using a combination of radionuclide bone scan examination and monoclonal protein studies. In individual cases which meet established criteria the histological confirmation and typing of amyloid is not needed.[10]

It should be emphasised that even though amyloid is not detected in the collected samples, the diagnosis of amyloidosis cannot be absolutely ruled out. This is due to a variable distribution of amyloid deposits, which may be diffused and pericellular but also nodular and patchy, with parts of the myocardium containing no amyloid at all.

The diagnosis is not always straightforward, especially if monoclonal gammopathy is present together with hereditary amyloidosis in patients with the systemic form of amyloidosis. This phenomenon has been reported in 3–10% of cases.[10,11]

THE CLINICAL PICTURE OF AND DIAGNOSTIC APPROACH TO CARDIAC AMYLOIDOSIS

Non-specific signs predominate in early amyloid cardiomyopathy. The amyloid deposits cause a slowly progressing thickening of the heart wall with increasing diastolic dysfunction, but the left ventricular ejection fraction remains stable for quite a long time. The fully developed disease is characterised by congestive heart failure with predominant right-sided heart failure symptoms including weakness, fatigue, weight loss or gain and shortness of breath. In chronic refractory heart failure, electromechanical dissociation or arrhythmia cause death in most cases.

A wide range of signs can be found on physical examination as most patients develop the systemic form of the disease. Common findings in systemic amyloidosis are hypotension (mostly orthostatic), dyspnoea, polyneuropathy, macroglossia, periorbital purpura, leg oedema, hepatomegaly, ascites and pleural effusion. Frequently, there are changes in heart rate (decreased or variable rate); patients may present with palpitations, syncope or even sudden death

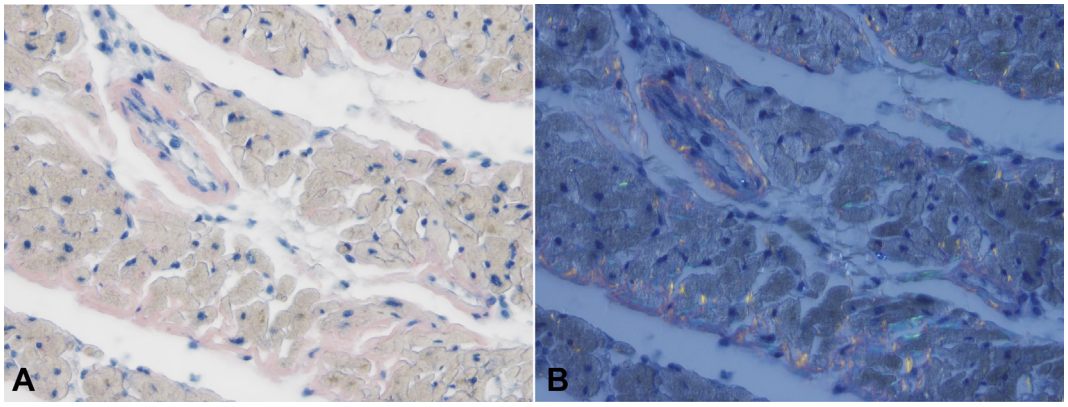

Fig. 1 Special histological staining. (A) Congo red with (B) polarising microscopy.

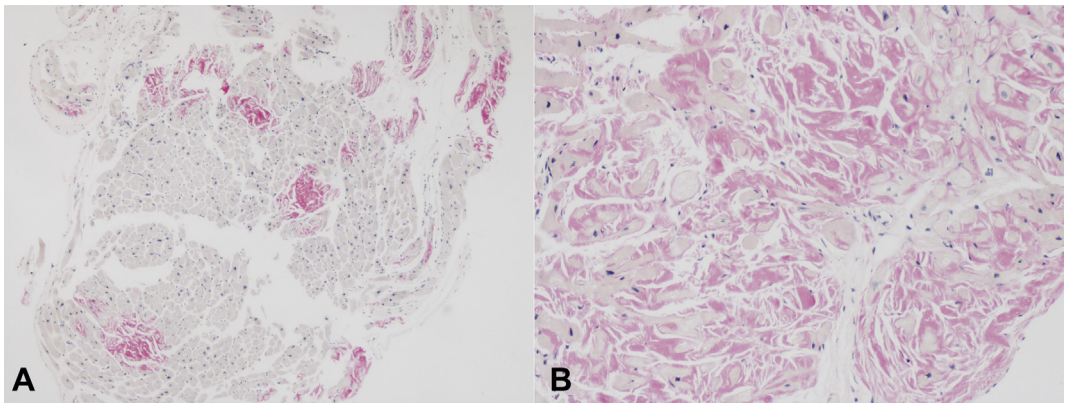

Fig. 2 Special histological staining, Sirius red. Variable severity of myocardial involvement (A), predominantly diffused and pericellular deposition of amyloid (B).