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Case report

Immunoglobulin light-chain amyloidosis – Diagnosed through electrocardiographic and echocardiographic features

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ABSTRACT

Introduction: Immunoglobulin light-chain (AL) amyloidosis is a systemic amyloidosis characterized by extracellular accumulation of fibrillary deposits composed of monoclonal immunoglobulin light chain fragments. Detection of the amyloid requires a special dye. The gold standard is Congo red stain. Clinical manifestation of the AL amyloidosis is variable and nonspecific. Amyloid deposits in cardiac issues lead to biventricular wall thickening. On the other hand, the amount of cardiomyocytes decreases, which manifests as a low QRS amplitude. The standard electro- and echocardiography may assist in the diagnosis of AL amyloidosis.

Aim: The aim of the study is to present the possibilities of using a standard electrocardiography and an echocardiography for diagnosis of a rare immunoglobulin AL amyloidosis.

Case study: This is the case of a 60-year-old woman who suffered from progressive fatigue, weight loss, diarrhea lasting for two years and recurrent syncope, hypotension, and dyspnea for six months. Routine diagnostic tests did not explain the cause of her symptoms. Electrocardiography revealed a low QRS voltage. An echocardiogram showed thickening of the left and right ventricular walls. The histological examination with Congo red staining revealed the amyloid deposits. The primary λ-light chain amyloidosis of heart, kidneys, autonomic nerves and soft tissue was diagnosed.

Results and discussion: We presented a typical case of immunoglobulin AL amyloidosis, which was detected thanks to characteristic electro- and echocardiographic findings.

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Conclusions: The coexistence of multiorgan dysfunction and the thickening of ventricular walls as shown by echocardiography combined with the lack of hypertrophy electrocardiographical features enables us to diagnose amyloidosis intravitally.

1. Introduction

Immunoglobulin light-chain (AL) amyloidosis is the most common type of systemic amyloidosis characterized by extracellular accumulation of fibrillary deposits, which is composed of monoclonal immunoglobulin light chain fragments synthesized by clonal plasma cells in the bone marrow. In most cases it is a primary disease, but may be associated with myeloma or other B-cell malignancy. It is considered to be a very rare disease even though its incidence is similar to the better-known Hodgkin disease.[1] It is estimated that the disease affects 5–12 people per 1 million per year. The diagnostic process starts from proving tissue amyloid accumulation. For that purpose, a tissue (usually subcutaneous abdominal fat tissue) biopsy is performed. Detection of the amyloid requires a special dye. The gold standard test is the Congo red stain. Amyloid deposits bind with the Congo red dye and exhibit the pathognomonic apple-green birefringence when viewed with a polarizing microscope. The next steps are as follows: identification of the amyloid precursor protein (monoclonal immunoglobulin light-chain), detection and differentiation of plasma cells dysplasia (primary or myeloma-associated) and defining organ involvement.

The AL amyloidosis affects many organs (most commonly kidney, heart, liver, gastrointestinal tract, nerves, and soft tissues), therefore the clinical manifestation is variable and nonspecific, which make the disease difficult to recognize. The most common symptoms are weight loss and fatigue, chronic diarrhea, progressive dyspnea, peripheral edema, hepatomegaly, ortostatic hypotension and proteinuria. In some cases (about 15% of patients), more specific symptoms, called 'red flags,' such as macroglossia, submandibular edema and 'raccoon eyes' (peri-orbital purpura) are present. When amyloidosis affects the heart, congestive heart failure, conduction abnormalities, arrhythmias, angina, syncope and sudden cardiac death may occur. Cardiac involvement is a leading cause of mortality due to electromechanical dissociation. The long-drawn elevation of cardiac troponins and the N terminal-pro brain natriuretic peptide (NT-pro BNP) is regarded as a typical change in cardiac amyloidosis, even at an early stage, as a result of the toxic effect of amyloids on myocytes and microvascular changes.

Amyloid deposits in cardiac tissue lead to biventricular wall thickening without ventricular enlargement visualized by the echocardiogram. Additionally, myocardial echogenicity increases ('granular sparkling'). The left ventricular ejection fraction is normal for a long time and diastolic dysfunction is dominant, although systolic dysfunction can be proved by tissue Doppler techniques. Wall thickening is often incorrectly described as hypertrophy, leading to a misdiagnosis of hypertrophic cardiomyopathy or hypertensive heart disease. The QRS voltage on 12-lead electrocardiography in amyloidosis is low unlike true ventricular hypertrophy. The combination of these electro- and echocardiographic findings strongly suggests a cardiac amyloidosis.

2. Aim

The aim of the study is a case report of a rare AL amyloidosis unrelated to multiple myeloma (primary amyloidosis), diagnosed on the basis of standard electrocardiography abnormalities and an echocardiography.

3. Case study

This is the case of a 60-year-old woman who suffered from progressive fatigue, weight loss (from 102 kg to 60 kg), diarrhea for two years and recurrent syncope, hypotension, dyspnea on exertion (NYHA III) for six months. She was hospitalized four months before admission to our department due to syncope as a complication of a right femur fracture. At the same time, myocardial infarction was diagnosed based on elevated levels of cardiac troponin T; however, angiography was not

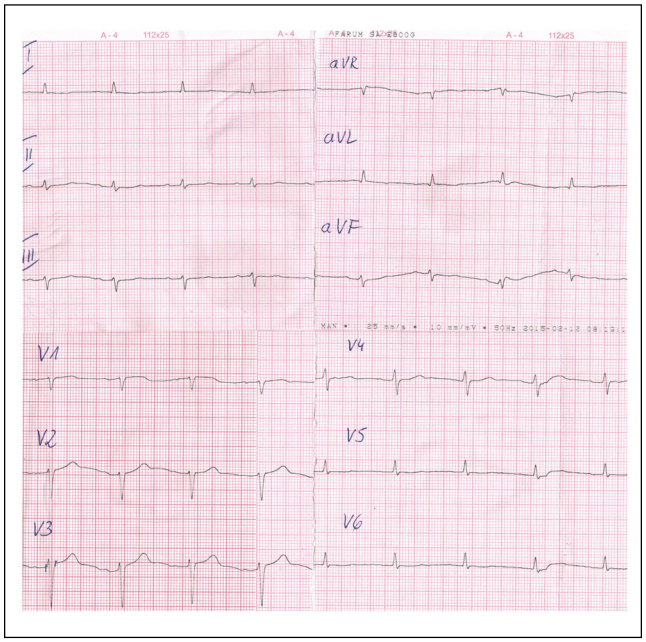

Fig. 1 – A 12-lead electrocardiogram of illustrating the low voltage limb QRS complexes, left anterior hemiblock and prolonged PR interval to 210 ms.

performed. Left ventricular symmetrical thickening was detected (diastolic thickness of interventricular septum and posterior wall was 14 mm) in echocardiography, therefore hypertrophic cardiomyopathy was suspected. Routine diagnostic tests did not explain the cause of the diarrhea and weight loss. The mechanism of syncope was not found.

On admission to our department, a physical examination revealed: a 2/6 grade protosystolic murmur, mild peripheral edema, regular heart rate 65 bpm, blood pressure 90/60 mmHg, bilateral rales on lung auscultation, and an enlarged bladder. Abnormalities observed in laboratory studies were: anemia, sideropenia, hypoalbuminaemia, proteinuria, reduced glomerular filtration rate and an elevated level of cardiac troponin (Table 1). Standard 12-lead electrocardiography revealed a normal sinus rhythm, prolonged PR interval to 210 ms, and a left anterior hemiblock. Low QRS voltage was notable (Fig. 1). A 24-h Holter ECG revealed paroxysmal atrial fibrillation. An echocardiogram showed: left and right ventricular walls thickening with increased echogenicity ('granular sparkling'), thickening of the interatrial septum, dilated atria, relatively small dimension of ventricles, normal ejection fraction, diastolic dysfunction (grade 2), mild mitral regurgitation and small pericardium effusion (Fig. 2, Table 2). A chest X-ray revealed

Table 1 – Laboratory tests.

Test/assay	Value	Reference value
Hemoglobin [g/dL]	9.8	12–17
Creatinine [mg/dL]	1.62	0.5–1.2
eGFRwg MDRD [mL/min/1.73 m^2]	34.57	>90
24-h urine total protein [g]	2.5 g	<250 mg
Albumin [g/dL]	2.5	3.5–5
Fe [μg/dL]	8	37–158
Troponin T [pg/mL]	259.8	<14
Free immunoglobulin λ chain [mg/L]	746	5.71–26.3
Free immunoglobulin κ chain [mg/L]	12.5	3.3–19.4
κ/λ ratio	0.02	0.26–1.65

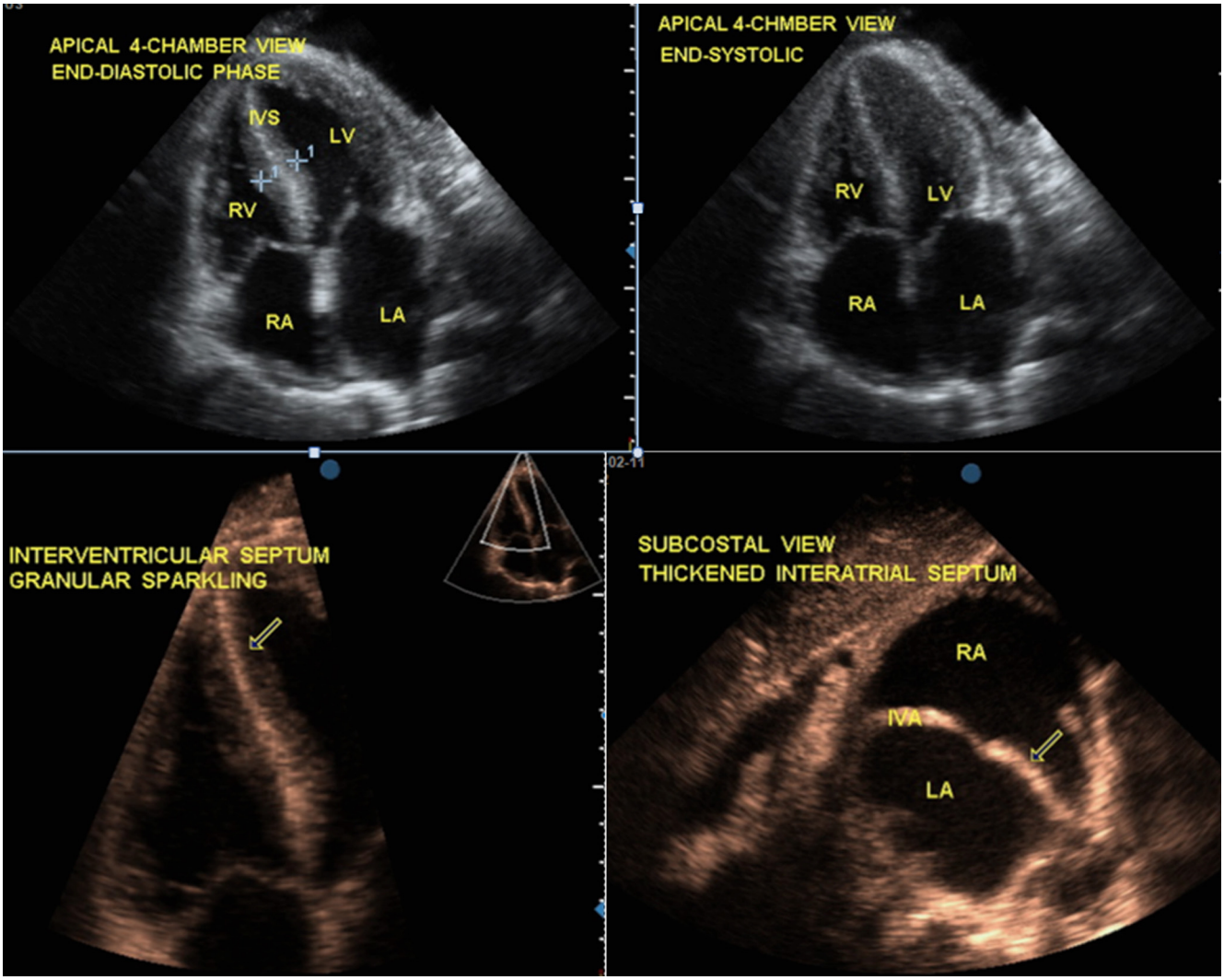

Fig. 2 – Echocardiograms showing biatrial dilatation, thick ventricular walls and interatrial septum, increased myocardial echogenity ('granular sparkling'), small pericardium effusion. Note that ventricular chambers are not dilated.

Table 2 – Clinical symptoms and abnormalities in additional tests present in patient.

Clinical symptoms	Electrocardiographic features	Echocardiographic features	Changes in laboratory tests	Microscopic examination
Fatigue	Low QRS amplitude in limb leads	Thickened left and right ventricular walls (IVS = 14–19 mm, PW = 14 mm, RV wall = 8 mm)	Anemia	Bone marrow aspirate: small increase in the percentage of plasma cells
Weight loss	Abnormal left axis deviation	Increased myocardial echogenicity ('granular sparkling')	Sideropenia	Subcutaneous abdominal fat biopsy: amyloid deposits
Chronic diarrhea	Left anterior hemiblock	Thickening of interatrial septum (6 mm)	Hypoalbuminaemia	
Hypotension	First-degree atrioventricular block	Enlargement atria (LA area 29 cm^2, RA area 26 cm^2)	Proteinuria	
Dyspnea	Paroxysmal atrial fibrillation	Small ventricular cavity size (EDD 40 mm, ESD 23 mm)	Reduced glomerular filtration rate	
Syncope		Preserved ejection fraction (LVEF 70%)	Elevated level of cardiac troponin	
'Raccoon eyes'		Diastolic dysfunction grade 2 (e′ = 5 cm/s, E/e′ = 15, E/A = 1.5)	Elevated level of free immunoglobulin λ-light chain	
Peripheral edema		Mild protosystolic mitral regurgitation	Bence Jones protein in urine	
Retention urine				
Protosystolic murmur				
Bilateral rales on lung auscultation				

left pleural effusion. An abdominal ultrasound revealed an enlarged bladder due to urine retention. As a result, amyloidosis was suspected.

The histological examination with Congo red staining of subcutaneous abdominal fat tissue revealed the amyloid deposits. Serum-free light chains assay showed an elevation of free λ with abnormal κ/λ ratio (Table 1). There was Bence Jones protein in the urine. The level of serum amyloid A was normal. A bone marrow biopsy demonstrated 9% plasma cells, which excluded myeloma as the cause. The primary λ-light chain amyloidosis of heart, kidneys, autonomic nerves and soft tissue was diagnosed according to a consensus opinion from the 10th International Symposium on Amyloidosis.[2] Before referring to the hematology center, the 'red flag' symptoms – 'raccoon eyes' and a cardiac arrest with a complete heart block occurred. After successful resuscitation, the patient was transferred to the intensive care unit, where she died after two days due to severe mechanical heart dysfunction (electromechanical dissociation). An autopsy with histological examination confirmed the diagnosis (Fig. 3).

4. Results

We presented a typical case of immunoglobulin AL amyloidosis, which was detected thanks to characteristic electro- and echocardiographic findings. The coexistence increased ventricular walls thickness and low voltage QRS and other findings suggested cardiac amyloidosis.

5. Discussion

The latest European Society of Cardiology guidelines on diagnosis and management of hypertrophic cardiomyopathy[3] include all cardiac diseases with increased left ventricular wall thickness (in adults more than or equal to 15 mm in one or more left ventricular myocardial segments) that is not solely explained by abnormal loading conditions, also cardiac amyloidosis. Diseases with ventricular wall thickening, for clinical use, can be classified according to the amplitude of QRS complexes. These can then be divided into diseases with high QRS amplitude (e.g. hypertension heart disease, aortic stenosis, hypertrophic cardiomyopathy caused by sarcoma protein gene mutations, Fabry disease, etc.) and diseases with low or normal QRS amplitude (e.g. amyloidosis, hemochromatosis, sarcoidosis). A low QRS amplitude may result from non-cardiac disease such as: obesity, emphysema or a large amount of fluid in the pericardium.

In the case of the described patient, the ventricular wall thickness was the result of amyloid deposition rather than cardiomyocytes hypertrophy. The low QRS voltage resulted from atrophy of the cardiomyocytes. Moreover, the 'granular sparkling' and septal thickening occurred. ''A diffuse hyperrefractile 'granular sparkling' appearance of the thickened myocardium'' was first described in 1981 by Siqueira-Filho[4] and may also be present in Danon disease. However, in that case a high voltage QRS can be observed.

The characteristic symptom is also a thickening of the interatrial septum.[5] If accompanied by a thickening of the

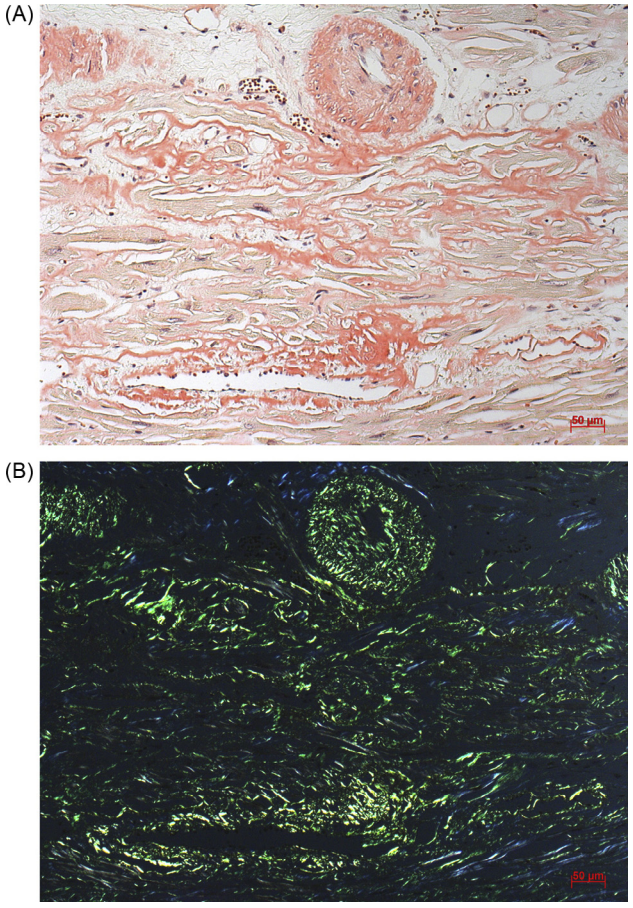

Fig. 3 – Histological examination of myocardial tissue (the fragment of a left ventricle wall). Congo red staining: (A) positive Congo red staining viewed in normal light; (B) apple-green birefringence viewed under polarized light (courtesy of Prof. Barbara Przybylska-Gornowicz and Małgorzata Jakubowska).

ventricular walls and valves' leaflets, the diagnosis of cardiac amyloidosis is almost certain. However, an isolated thickened interatrial septum may be a result of neoplastic lesions.

6. Conclusions

1. The case reported above shows difficulties in the diagnostic process of AL amyloidosis – a rare disease caused by plasmocytes dyscrasia. The base of recognition is microscopic examination under polarized light using specific staining (Congo red).
2. The coexistence of multiorgan dysfunction and the thickening of ventricular walls as shown by echocardiography combined with the lack of hypertrophy electrocardiographical features enables us to diagnose amyloidosis intravitally.
3. In cases of unexplained progressive cachexia, chronic diarrhea (especially with accompanying proteinuria), elevated level of cardiac troponin, heart murmur, syncope or hypotension, amyloidosis should be taken into consideration.

Conflict of interest

None declared.

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