Patient with multiple myeloma and suspected cardiac amyloidosis (RCD code: III-3A.2a)

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Abstract

49 year-old patient with multiple myeloma diagnosed a year earlier, after a few cycles of chemotherapy was admitted to hospital with heart failure symptoms accompanied by a rapid atrial flutter. Echocardiography revealed eccentric hypertrophy of the left ventricle and reduced ejection fraction approx. 20% and non sustained ventricular tachycardia episodes in the Holter ECG. Due to the gradually deteriorating patient’s condition electrical cardioversion was performed restoring sinus rhythm. Applied pharmacological treatment brought relief of symptoms reported at admission. To clarify the etiology of heart failure coronary angiography was performed excluding the presence of coronary artery disease. Because of the frequent occurrence of amyloidosis in patients with multiple myeloma, the amyloid cardiomyopathy was suspected and the investigation in that direction was started. Histology samples of abdominal fat and gums mucous in a hematoxylin and eosin and Sirius red staining showed no signs of amyloidosis. However, bone marrow biopsy revealed the presence of protein corresponding to the extracellular amyloid deposits. The patient died a few months later in hematology clinic due to severe multiple organ failure associated with generalized amyloidosis. JRCD 2015; 2 (2): 56–59

Key words: amyloidosis, heart failure, myeloma multiplex

Case presentation

49 year old patient with multiple myeloma (diagnosed over a year ago), after several cycles of chemotherapy was admitted to the Cardiology Department in Chrzanów with symptoms of cardiac decompensation associated with atrial flutter. Previously hospitalized in another hospital where he went because of heart palpitations associated with rapid atrial flutter 140 bpm.

First patient’s health problems appeared in the November 2012 r. He was taken to the district hospital due to severe pain around the thoraco-lumbar (Th-L) region after lifting a heavy object. Compression fracture of Th 9 body was found with the pouches of the bone masses into the spinal canal with compression on the spinal cord. Osteolytic foci in the vertebral bodies Th4 and Th 11 was also revealed. The bone marrow puncture was performed in which there were no signs of suspected multiple myeloma. Further diagnosis focused on trying to find a primary cancer focus that was the alleged source of the neoplastic spread and the above described osteolytic lesions in the spine, collarbone, pelvis and pathological fracture of humerus and vertebra Th 9. Despite the implementation of numerous imaging tests [computed tomography (CT) thorax, CT abdomen, panendoscopy] the origin of neoplastic process was not found. Laboratory tests revealed slight anemia [red blood cells (RBC) of 4.0 M/µl, hemoglobin concentration (HGB) of 11.8 mg/dl, hematocrit (HCT) of 35.4%), decreased levels of parathyroid hormone (PTH) – 4.9 pg /ml, increased erythrocyte sedimentation rate (ESR) – 32 mm/h, a hypercalcemia (Ca2+ – 1.37 mmol/l). Tumor markers (AlphaPhetoprotein – AFP, cancer antigen125-CA125, prostate specific antigen – PSA) were negative. In electrophoresis, there was no presence of a monoclonal protein. The next step was nuclear diagnostic (January 2013). After single-photon emission computed tomography (SPECT) of the chest the bone remodeling was found (Figure 1). The image required differentiation between the spread of cancer and metabolic bone disease (hyperparathyroidism).

The patient was referred to department of endocrinology with suspected metabolic bone disease and eventually to department of hematology where bone marrow biopsy was acquired. Multiple myeloma was diagnosed. Patient was qualified to chemotherapy CTD (cyclophosphamide, thalidomide, dexamethasone), with a plan to implement high-dose chemotherapy supported by autologous stem cells transplantation. Due to the lack of satisfactory response second line treatment was implemented – bortezomib, cyclophosphamide, dexamethasone. In October 2013 cardiovascular compli-
Patient with multiple myeloma and suspected cardiac amyloidosis

In laboratory studies slightly elevated potassium levels (5.3 mmol/l), aspartate aminotransferase (AST) (184 U/l), alanine aminotransferase (ALT) (350 U/l), alkaline phosphatase (118 U/l), gamma-glutamyltransferase (GGT) (120 U/l), direct bilirubin (27.3 micromol) and C-reactive protein (CRP) (92.5 mg/l) were observed. Echocardiography showed increased dimension of cardiac chambers with eccentric left ventricular hypertrophy and reduced ejection fraction (about 20%) with septal akinesia and hypokinesia of other walls (Figure 3). Mild mitral and tricuspid regurgitation, right ventricular systolic pressure (RVSP)- about 48 mm Hg. A small amount of fluid in pleural cavities.

The Holter-ECG test revealed the presence of non-sustained ventricular tachycardia (Figure 4).

Due to the progressively deteriorating condition of the patient successful electrical cardioversion was performed. Coronary angiography was performed excluding the presence of occlusions in the coronary arteries. Taking the whole clinical picture into account a suspicion of amyloid cardiomyopathy was made. Serum protein electrophoresis was performed revealing no presence of monoclonal protein. In a urine sample, there was no Bence Jones protein. Histological samples of the abdominal adipose tissue and the gingival mucosa in a study with hematoxylin and eosin showed no signs of amyloidosis. Sirius red staining did not reveal the presence of amyloid in the tissue. Applied treatment with a beta-blocker, loop diuretic, aldosterone antagonist and amiodarone resulted in a gradual improvement of his general condition. The patient in good general condition was discharged home. Two months later the echocardiography showed no improvement in left ventricular contractility. No further follow-up was available in this patient.
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Review of literature

Amyloidosis is a rare disease due to extracellular deposition of fibrils (beta-sheet structure protein) in tissues and organs. They are characterized by apple-green birefringence in polarized light after Congo Red staining [1]. Light-chain amyloidosis is the most frequent type. It affects 10 patients per million persons per year. 10% – 15% of patients with myeloma or Waldenström macroglobulinemia have AL amyloidosis. Involvement of the heart varies with the type of disease and in light chain amyloidosis (AL) is present in about 50% of cases [2]. Myocardial deposition of amyloid leads to organ dysfunction. The proteins allow accumulation and disruption of cardiac function. Myocardial thickening, diastolic dysfunction and restrictive cardiomyopathy can occur. Median 1 year survival without treatment is less than 1% in patients with heart infiltration [3]. QRS voltages at all limb leads less than 5mm with poor R wave progression in the chest leads (pseudoinfarction pattern) are characteristic for cardiac AL amyloidosis (in up to 50% of patients) [4]. Atrial fibrillation or flutter is seen in about 20% [5].

Echocardiography is a basic method for the diagnosis of patients with cardiac amyloidosis. Increased LV wall thickness on echocardiography, with a “granular sparkling” appearance of the myocardium, normal LV cavity, and enlarged atria with a restrictive filling pattern, is a classic feature of cardiac amyloidosis.[6,7]

Low-voltage complexes QRS with increased left ventricular mass (determined echocardiographically) are characteristic for cardiac amyloidosis with a high sensitivity and specificity of 72% and 91%. [5]. Cardiac Magnetic Resonance is one of the most accurate methods that could detect infiltrated heart muscle in systemic amyloidosis (late gadolinium enhancement) [8]. On the basis of the myocardium biopsy it was established that noninvasive magnetic resonance can be an effective tool to diagnose or rule out cardiac amyloidosis with good sensitivity and specificity (80% and 94%) [9]. Laboratory tests can be also useful. Immunofixation can determine the presence of abnormal proteins in blood or urine. A free light chain assay is used order to quantify the amount of abnormal proteins. A bone marrow biopsy can be performed to examine the number of plasma cells [10]. On the other hand endomyocardial biopsy are not common procedure. A histological analysis of the abdominal fat can be diagnostic for amyloidosis (characteristic apple green birefringence seen under polarized light after staining tissue with Congo red) [11]. Treatment of AL amyloidosis is based on chemotherapy against B-cells producing light chain proteins that amyloid is formed of [2].

In this case, the etiology of observed was not clear at the beginning. The studies provided ambiguous information. Image ECG and echocardiography examination showed no characteristics features for amyloidosis. In addition, abdominal adipose tissue and gums biopsy Sirius red stained were negative. According to the available sources sensitivity of the histological analysis varies between 74–95% for abdominal fat [12, 13, 14] and 86‑88% for the gingival mucous[15, 16]. However, there was a positive result of microscopic analysis of bone biopsy. The question remains whether such a set of data can be available to identify atypical forms of cardiac amyloidosis? Magnetic resonance certainly would bring a lot of information. However, due to the lack of patient contact with the local center, such research has not been done. Another reason, which was taken into account was tachyarrhythmia associated cardiomyopathy. Literature describes that after a short time, rapid heart rate can lead to heart failure. However, changes in ejection fraction are reversible.

Figure 3. Echocardiography: a – parasternal long axis view, b- short axis view, c- four chamber view, d – two chamber view

Figure 4. Holter ECG – Non sustained ventricular tachycardia
and disappear quickly after normalization of rhythm [17, 18]. In the present case after about 2 months of rhythm control there has been no improvement in cardiac contractility. Another cause taken into account was toxic cardiac injury associated with chemotherapy. According to sources, both cyclophosphamide and bortezomib may have cardiotoxic effects [19, 20, 21, 22]. Another point worth discussing are the indications for implantable cardioverter defibrillator (ICD). European guidelines concerning ICD therapy does not provide an opinion on the use of such devices in patients with cardiac amyloidosis. In addition, unfavorable prognosis for survival for over a year in the case of cardiac amyloidosis is another obstacle to the routine use of ICD. Reports in the literature indicate that patients may benefit from the use of these devices [23]. Additionally, description of cases are available, in which the survival of patients with heart amyloidosis dates back even a few years thanks to adequate ICD intervention [24]. However, there are works that claim that ICD implantation, despite adequate therapy does not prolong the lives of patients [25]. Due to the small number of patients and described incompatible data, these issues still need further investigation.

**Patient management and follow-up**

Despite initiating optimal heart failure medical therapy no long-term improvement was achieved. She eventually died four months later, from multiple organ failure in the course of systemic amyloidosis.

**References**