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ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА АМИЛОИДОЗА СЕРДЦА И ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ

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Differential Diagnosis of Cardiac Amyloidosis and Hypertrophic Cardiomyopathy

Резюме

Диагностика и дифференциальная диагностика амилоидоза сердца и гипертрофической кардиомиопатии в ряде случаев затруднительна, что подтверждается представляемым клиническим наблюдением. Пациент А., 67 лет, с 59 лет в течение 7 лет страдал артериальной гипертонией с максимальными цифрами артериального давления 170/100 мм рт. ст., получал антигипертензивную терапию. С января 2018 г. (с 65 лет), на фоне самопроизвольной стабилизации цифр артериального давления стала беспокоить одышка при подъеме на второй этаж, подъеме тяжестей, удушье в ночные часы, отеки голеней, стоп, в связи с которыми обратился к врачу. При обследовании на электрокардиограмме отмечен низкий вольтаж комплексов QRS в отведениях от конечностей, отсутствие нарастания амплитуды зубца r в $V_{1–3}$. При эхокардиографии выявлено утолщение межжелудочковой перегородки и задней стенки левого желудочка до 1,9 см без обструкции выходного отдела левого желудочка, рестриктивным типом диастолической дисфункции, дилатация левого и правого предсердий, умеренная легочная гипертензия, умеренное количество жидкости в полости перикарда. При магнитно–резонансной томографии сердца выявлена картина, типичная для амилоидоза сердца: диффузное субэндокардиальное контрастирование миокарда обоих желудочков при отсутствии нарушения локальной сократимости, увеличение толщины миокарда во всех сегментах, гидроперикард. При биопсии кожи и подкожно–жировой клетчатки с окраской Конго красным и поляризационной микроскопией амилоидных отложений не выявлено. При генетическом исследовании мутаций в гене транстиретина, ответственных за транстиретиновый амилоидоз (ATTR–амилоидоз), не выявлено. При секвенировании 10 генов, кодирующих саркомерные белки миокарда, в гене *MYBPC3* выявлена мутация c.3197C> G (p.Pro1066Arg) в гетерозиготном состоянии, ранее описанная у пациентов с гипертрофической кардиомиопатией славянского происхождения. Каскадный семейный скрининг на носительство мутации не проводился в связи с тем, что отца пациент не знал, мать умерла в возрасте 75 лет от сердечной недостаточности, единственный сын скончался от несчастного случая за полгода до обращения пациента за врачебной помощью. 15.02.2019 г. пациент перенёс остановку кровообращения с успешными реанимационными мероприятиями. С целью вторичной профилактики внезапной сердечной смерти 22.02.2019г. проведена имплантация однокамерного кардиовертера–дефибриллятора. Несмотря на проводимую терапию, пациент скончался в марте 2019г. от прогрессирующей сердечной недостаточности. В представленном клиническом случае описан диагностический поиск, в котором при магнитно-резонансной томографии заподозрена амилоидная кардиомиопатия, не получившая морфологического подтверждения в биоптатах внесердечной локализации, но на основании клинико-инструментальных и молекулярно-генетических методов была подтверждена гипертрофическая кардиомиопатия, обусловленная мутацией c.3197C>G (p.Pro1066Arg) в гене *MYBPC3*. Картина, харак-

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терная для амилоидоза сердца, описанная у пациента при инструментальных методах обследования, может быть обусловлена нарушением процессов аутофагии, ранее описанных при ряде мутаций в гене *MYBPC3*, что может приводить к накоплению амилоидоподобных включений в кардиомиоцитах. Для дифференциальной диагностики кардиомиопатий в сложных случаях может требоваться эндомиокардиальная биопсия. Не исключена возможность сосуществования генетически обусловленной гипертрофической кардиомиопатии и амилоидного поражения сердца.

Ключевые слова: *амилоидоз сердца, амилоидная кардиомиопатия, гипертрофическая кардиомиопатия, мутация MYBPC3, транстиретин, прогрессирующая сердечная недостаточность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Diagnosis and differential diagnosis of cardiac amyloidosis and hypertrophic cardiomyopathy is difficult in some cases, which is confirmed by the presented clinical observation. The patient A., 67 years old, from the age of 59 for 7 years suffered from arterial hypertension with a maximum blood pressure of 170/100 mmHg, received hypotensive therapy. Myocardial infarction, a history of stroke denies. Since January 2018, at the age of 65, against the background of spontaneous stabilization of blood pressure figures, shortness of breath when climbing to the 2nd floor, lifting weights, suffocation at night, swelling of the shins, feet, in connection with which I turned to a doctor. When examined on an electrocardiogram, a low voltage of QRS complexes in the leads from the extremities was noted, there was no increase in the amplitude of the r wave in V1–3. Echocardiography revealed a thickening of the interventricular septum and the posterior wall of the left ventricle up to 1.9 cm without obstruction of the outlet of the left ventricle, restrictive type of diastolic dysfunction, dilation of the left and right atria, moderate pulmonary hypertension, moderate amount of fluid in the pericardial cavity. Magnetic resonance imaging of the heart revealed a pattern typical of cardiac amyloidosis: diffuse subendocardial contrast of the myocardium of both ventricles in the absence of local contractility disorders, increased myocardial thickness in all segments, hydropericardium. Biopsy of the skin and subcutaneous fat with Congo red staining and polarization microscopy revealed no amyloid deposits. No mutations in the transthyretin gene responsible for transthyretin amyloidosis (ATTR–amyloidosis) were detected during the genetic study. Sequencing of 10 genes encoding myocardial sarcomeric proteins in the *MYBPC3* gene revealed a mutation c.3197C >G (p.Pro1066Arg) in a heterozygous state, previously described in patients with hypertrophic cardiomyopathy of Slavic origin. Cascade family screening for the mutation was not carried out due to the fact that the patient did not know the father, the mother died at the age of 75 from heart failure, the only son died from an accident six months before the patient's treatment. On 15.02.2019, the patient suffered a circulatory arrest with successful resuscitation measures. For the purpose of secondary prevention of sudden cardiac death, a single–chamber cardioverter-defibrillator was implanted on 22.02.2019. Despite the ongoing therapy, the patient died in March 2019. from progressive heart failure. Thus, a clinical case is presented where magnetic resonance imaging suspected amyloid cardiomyopathy, which did not receive morphological confirmation in biopsies of extra–cardiac localization. Hypertrophic cardiomyopathy caused by mutation c.3197C >G (p.Pro1066Arg) in the *MYBPC3* gene was confirmed on the basis of clinical and instrumental and molecular genetic methods. The pattern characteristic of cardiac amyloidosis described in this patient with instrumental examination methods may be due to a violation of autophagy processes previously described with a number of mutations in the *MYBPC3* gene, which may lead to the accumulation of amyloid-like inclusions in cardiomyocytes. For differential diagnosis of cardiomyopathies in complex cases, endomyocardial biopsy may be required. The possibility of coexistence of genetically determined hypertrophic cardiomyopathy and amyloid heart disease is not excluded.

Key words: *amyloidosis of the heart, amyloid cardiomyopathy, hypertrophic cardiomyopathy, MYBPC3 mutation, transthyretin, progressive heart failure*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BP — blood pressure, SCD — sudden cardiac death, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, DCMP — dilated cardiomyopathy, ICD — implantable cardioverter defibrillator, CT — computed tomography, LV — left ventricle, LA — left atrium, IVS — interventricular septum, MV — mitral valve, MSCT — multispiral computed tomography, IAS — interatrial septum, MRI — magnetic resonance imaging, HOCM — hypertrophic obstructive cardiomyopathy, SPECT — single-photon emission computed tomography, RV — right ventricle, RA — right atrium, PASYS — pulmonary artery systolic pressure, HF — heart failure, HFwEF — heart failure with preserved ejection fraction, LVEF — left ventricular ejection fraction, CHF — chronic heart failure, HR — heart rate, ECG — electrocardiogram, EchoCG — echocardiography, BNP — brain natriuretic peptide, MYBPC3 — myosin-binding protein C, NYHA — New York Heart Association, ATTR — transthyretin amyloidosis, wtATTR-CMP — transthyretin cardiomyopathy, wild type

Introduction

Differential diagnosis of primary hypertrophic cardiomyopathy (HCM) and its phenocopies, including cardiac amyloidosis, is often challenging, as both conditions have similar clinical symptoms and manifestations seen during imaging studies. Both conditions can be asymptomatic for a long period of time, or can manifest as steady progression of heart failure, arrhythmias and/or impaired conductivity; sometimes they can cause sudden cardiac death (SCD) [1].

Hypertrophic cardiomyopathy

Typically, HCM is caused by pathogenic variants of genes encoding contractile proteins of sarcomere — myosin (MYH7), myosin-binding protein C (MYBPC3), actin (ACTC), troponin (TNNI3, TNNT2, TNNC). It was found out that *MYBPC3* mutations are the most common cause of HCM, they account for approximately a half of identified mutations [2].

According to epidemiological studies, the incidence of HCM is 1:500 in general population; in age groups it varies from 1:500 to 1:200 [1]. When using the most sensitive imaging techniques (MRI, CT) and in a wider use of genetic testing and cascade screening of first-degree relatives, the incidence of HCM reaches 0.6 % (1:167) [1, 2].

The diagnostic criterion of HCM in adults is left ventricle (LV) wall thickening in at least one segment of ≥ 15 mm (with the use of any visualizing method — echocardiography (EchoCG), MRI or CT), which cannot be explained by a higher pressure-induced load alone. In proband's relatives, the diagnostic criterion of HCM is LV wall thickening of 13 mm [3, 4]. A long-lasting history of arterial hypertension (AH) requires differential diagnosis of HCM and LV myocardial hypertrophy (LVH) with increased blood pressure (BP). For a long time, HCM has been a diagnosis by exclusion, which was not possible with a history of AH. In HCM, LV myocardial wall thickening is caused not by pressure-induced load. AH comes with a higher afterload. LVH is diagnosed in 68 % of patients with AH. Hypertension disease at early remodeling stages can be associated with some LVH asymmetry, while at later stages LVH is symmetric. All major types of LV remodeling can be observed in patients with AH. In terms of cardiovascular complications, the most unfavorable types are concentric and eccentric LVH [5-7].

The current idea is that patients with AH can have HCM in the presence of at least one of the following criteria:

1. An indication of a family history of HCM or SCD at a young age in first-degree relatives, requiring a genetic test in order to establish LVH ethology.
2. A mismatch between the rate of LVH (maximum wall thickness of ≥ 15 mm) or recent mild or moderate AH with adequate patient compliance, as well as the absence of other causes which can lead to a similar stage of LVH. A possible diagnostic criterion of HCM with concurrent AH is LV myocardial thickness of ≥ 20 mm, with the myocardial thickness of 15–20 mm being a "gray zone" [3, 8, 9].

HCM can be a manifestation of some metabolic or neuromuscular diseases, as well as of Noonan and LEOPARD syndrome [10].

Table 1. *Clinical variants of the course of HCM [3]*

Variant	Description
Sudden cardiac death	Can occur with any variant of the course of HCM, including without previous symptoms (most often occurs in young patients < 35 years old, including athletes).
Asymptomatic course	Occurs in patients with an initially non — obstructive form of HCM (a small degree of myocardial hypertrophy, without concomitant MV abnormalities). The life expectancy of these patients as in the general population is 75 years or more.
Symptomatic stable (against the background of drug therapy) benign course	1. in patients with an initially non–obstructive form of HCM 2. with HOCM with a small degree of obstruction of LVOT.
Symptomatic complicated course of HCM manifests itself	1. atrial fibrillation — paroxysmal, persistent or permanent (from 25 to 30 %), associated with heart failure of varying severity and an increased risk of thromboembolic complications, including stroke 2. CHF — the appearance of shortness of breath, weakness, fatigue, palpitations. An increase in the severity of CHF to c III–IV FC (NYHA with preserved LV systolic function 3. angina syndrome (including atypical pain syndrome) or pain–free ischemia. Myocardial ischemia in HCMP can develop type 2 MI.
Symptomatic course with negative remodeling	1. "Final stage": further progression of the phenomena of chronic heart failure associated with negative remodeling and pronounced systolic and/or diastolic LV dysfunction. 2. Development of apical LV aneurysm — LV cavity obliteration by thickened myocardium in the middle part divided the chamber into 2 compartments with apical LV scar formation due to hydrodynamic lesion (a rare variant of the course of HCM).

Note: CHF — chronic heart failure, FC — functional classes, HCM — hypertrophic obstructive cardiomyopathy, HOCM — hypertrophic obstructive cardiomyopathy, MV — mitral valve, LVOT — left ventricular outflow tract, MI–myocardial infarction, NYHA — New York Heart Association, SCD — sudden cardiac death

Routine genetic testing in patients with HCM, restrictive cardiomyopathy (RCM), marked LVH is becoming more and more apparent, since early diagnosis and timely initiation of specific therapy are determinative factors which can modify the course of rare diseases [11].

HCM has an array of clinical manifestations (Table 1).

The management of HCM includes drug therapy, endovascular interventions, surgery and non-surgical methods to reduce a hypertrophic interventricular septum (IVS), mechanical circulatory support, heart transplant.

Cardiac amyloidosis and amyloid cardiomyopathy are HCM phenocopies.

Amyloid Cardiomyopathy

Systemic amyloidoses is a group of infiltrate diseases characterized by extracellular deposits of amyloid protein in tissues. This protein can deposit virtually in any organ and tissue, including heart, kidneys, liver, sympathetic nervous system, and impair their normal functions. Heart involvement manifests itself through amyloid infiltration of the myocardium and is a major factor impacting the diagnosis in systemic amyloidoses. Amyloid deposition around cardiac myocytes leads to an increased myocardium thickness, systolic/diastolic dysfunction, arrhythmia, impaired conductivity [1]. The most specific form is diffuse pseudohypertrophy with restriction and reduced left ventricle ejection fraction (LVEF), but without LV dilatation. Currently, there are nine precursor proteins that cause cardiac amyloidosis: immunoglobulin light chains (usually λ–AL–amyloidosis), immunoglobulin heavy chains (AH–amyloidosis), transthyretin (ATTR–amyloidosis), serum amyloid A (AA–amyloidosis), mutant apolipoprotein A I (AApoA I–amyloidosis), β_2–microglobulin A (β2M–amyloidosis), wild transthyretin (ATTRwt–amyloidosis), mutant transthyretin (ATTRm–amyloidosis), atrial natriuretic factor (AANF–amyloidosis) [6].

Heart is involved mostly in AL–, ATTR–, AA–amyloidosis [4].

Clinically, cardiac amyloidosis can resemble the following conditions:

1. RCM is a classical manifestation of cardiac amyloidosis, it being associated with diffuse myocardial infiltration with amyloid aggregates. Signs of RCM: restrictive diastole impairment, atrial dilatation. Over time, patients have aggravated LV pseudohypertrophy, and this feature distinguishes amyloidosis from idiopathic RCM.
2. HCM is a less common manifestation of cardiac amyloidosis and can resemble HOCM (including systolic movement of anterior MV leaflet).
3. Unlike the previous two variants, dilated cardiomyopathy (DCM) is completely uncommon for cardiac amyloidosis. DCM can be caused by myocardial ischemia due to small artery involvement. Also, the possibility of a combination of idiopathic DCM and amyloidosis is assumed.
4. A combination of the signs of hypertrophy, restriction and severe systolic dysfunction is a common phenotype in advanced cardiac amyloidosis.
5. Persistent minimal structural and functional EchoCG changes are one of the possible masks of amyloidosis [5].

According to the National Amyloidosis Centre, the incidence of amyloidosis in the United Kingdom is approximately 0.8 per 100,000 people [7]. Amyloidosis is known to cause 9 % of diagnosed HCM cases, and its incidence grows with the respondents' age (from 1 % at the age of 40–49 years old to 26 % at the age of over 80 years old). Genetic testing (including identification of transthyretin (TTR) gene mutations) should be considered for all patients with HCM phenotype [6].

Cardiac amyloidosis detection is a colossal issue. Very often, late diagnosis is a result of a number of non-specific manifestations. An array of clinical symptoms can vary from an asymptomatic disease to terminal heart failure (HF). The most common signs are fatigue, shortness of breath, and swelling of lower limbs. Also, dizziness, anginal retrosternal pain, peritoneal dropsy, and pain in right hypochondrium are not rare. Syncopic episodes can be caused by vegetative disorders, reduced cardiac output due to the poor ability of the cardiovascular system to increase the heart rate (HR) and vascular tone and, more rarely, by ventricular arrythmias, or a combination of both [8].

Amyloid cardiomyopathy can be diagnosed directly by biopsy of the myocardium or indirectly by an echocardiographic or MRI pattern of cardiac involvement in the presence of histological confirmation of extracardiac amyloidosis. ECG changes and cardiac biomarkers can confirm cardiac involvement, but they are non-specific. 90 % of patients with amyloidosis have changes observed during ECG. Very often, despite thickened LV walls seen during visualization, ECG wave voltage is reduced as a result of amyloid infiltration (mass-voltage dissociation), thus making it possible to suspect infiltration and not primary HCM. The pattern of pseudoinfarction of the lower LV wall or the septum area with Q-waves in two adjacent leads in the absence of any signs of subepicardial ischemia can also be observed in AL– и ATTR–amyloidosis. Amyloidosis can be suspected on the basis of EchoCG results. Amyloid accumulates in the myocardial interstitial tissue as nodal deposits and branching fibres, giving a spotty

(grainy) pattern. However, this sign has very low specificity due to the variability of interpretations by various specialists [1]. In addition to a spotty pattern, an EchoCG pattern of heart amyloidosis can present with dilatation of both atria, thickened walls (LV, right ventricle (RV), and interatrial septum (IAS)), thickened valve leaflets and pericardial effusion.

Heart MRI is very important in detection of an infiltrative cardiac pathology. Unlike EchoCG, MRI results are independent of an acoustic window [1]. Images with late enhancement show a typical diffuse subendocardial accumulation of gadolinium-based contrast agent, distinguishing heart amyloidosis from other cardiomyopathy types. Together, the commonly used methods have the accuracy of 97 % in detection of heart amyloidosis [1, 3].

It is recommended that amyloid cardiomyopathy is diagnosed with the use of planar nuclear scintigraphy in combination with single-photon emission computed tomography (SPECT). This examination is highly sensitive (99 %) and allows differentiating amyloidosis and other heart pathologies [7, 9].

Amyloid cardiomyopathy screening (including transthyretin cardiomyopathy) should be performed in all patients with HCM over 50 years of age. It can boost the efficiency of early diagnosis, which is essential for efficient therapy of the disease, where delayed detection and correct diagnosis still take decades [1, 6].

Successful differential diagnosis of genetically caused HCM, heart failure with preserved LVEF (HFpEF), and amyloidosis is possible with the use of the online calculator EstimATTR for the assessment of the probability of wild transthyretin cardiomyopathy (wtATTR–CMP) [12]. The patient data are entered into the calculator, including presence of heart failure, sex, age, cardiac (HFpEF; thickened LV wall; increased cardiac marker levels (troponin T, I, brain natriuretic peptide (BNP), brain natriuretic peptide precursor (NT–proBNP)); impaired cardiac conductivity (including His bundle blockade); atrial arrhythmia (including atrial flutter and fibrillation); pericardial effusion) and extracardiac manifestations (carpal tunnel syndrome; lumbar spinal stenosis; degenerative disorder of the shoulder, knee and/or hip joints; non-traumatic tendon rupture of biceps/heel tendon, or a history of surgical reconstruction; polyneuropathy (nondiabetic). The resulting factor value of over 1 means that the probability of wtATTR–CMP is higher than the probability of HF from other causes. The level of suspicion shows the probability of wtATTR–CMP-induced HF in an individual hypothetical patient vs. a patient with non-amyloid HF. The modelled probability reflects the probability of wtATTR–CMP-induced HF among general populations of patients with HF. Also, it is recommended to detect amyloidosis using a test for free lambda and kappa immunoglobulin light chains [7].

Despite all the above non-invasive methods, the golden standard of amyloidosis diagnosis is histological confirmation of amyloid deposition with Congo red staining and identification of typical apple-green double reflection with polarization microscopy. The sensitivity of endomyocardial biopsy reaches 100 %, while the sensitivity of subcutaneous adipose tissue biopsy is just 45 % and 15 % for genetical and wild ATTR–amyloidosis, respectively. If amyloidosis is confirmed, it should be typed. Differential diagnosis of genetic and wild ATTR–amyloidosis is performed using genetic typing [1, 9].

The therapy of any type of amyloidosis is divided into pathogenic (anti-amyloid therapy, the purpose of which is to reduce production and excretion of precursor proteins) and syndrome-based (symptomatic) [7].

Below is a case study of a patient with a challenging differential diagnosis of hypertrophic cardiomyopathy and heart amyloidosis.

Case Study

Patient A., 67 years old; AH since the age of 59 years old, the highest AH values were 170/100 mm Hg, a regular user of antihypertensives. A history of myocardial infarction, acute cerebrovascular event — denies. From the age of 65 years old, the patient has had shortness of breath during physical exercises; he did not undergo examination or treatment. At the age of 66 years old, EchoCG revealed marked symmetric concentric hypertrophy of LV myocardium with the wall thickness of up to 18 mm, hypertrophic papillary muscles without outflow tract obstruction, diffuse hypomotility with LVEF of 50 % dilatation of left atrium (LA) and right atrium (RA), restrictive diastolic LV dysfunction, grade II mitral regurgitation, grade II tricuspid regurgitation, moderate pulmonary hypertension. He has been taking Bisoprolol 5 mg daily, Verospiron 25 mg daily, Torasemide 10 mg daily, Perindopril 2.5 mg daily, Atorvastatin 10 mg/daily, for 5 months. Due to the therapy, the condition was satisfactory, shortness of breath reduced. However, the patient noted some episodes of AH reduction to 90/60 mm Hg, causing poor general condition. The patient stopped taking medications at the age of 67 years old (a year after therapy initiation); after that, the condition worsened: shortness of breath at minimal physical activity, swelling of lower limbs. Due to a negative trend, the patient was hospitalised on February 7, 2019 to the Federal State Budgetary Institution National Medical Research Centre for Cardiology of the Ministry of Health of the Russian Federation.

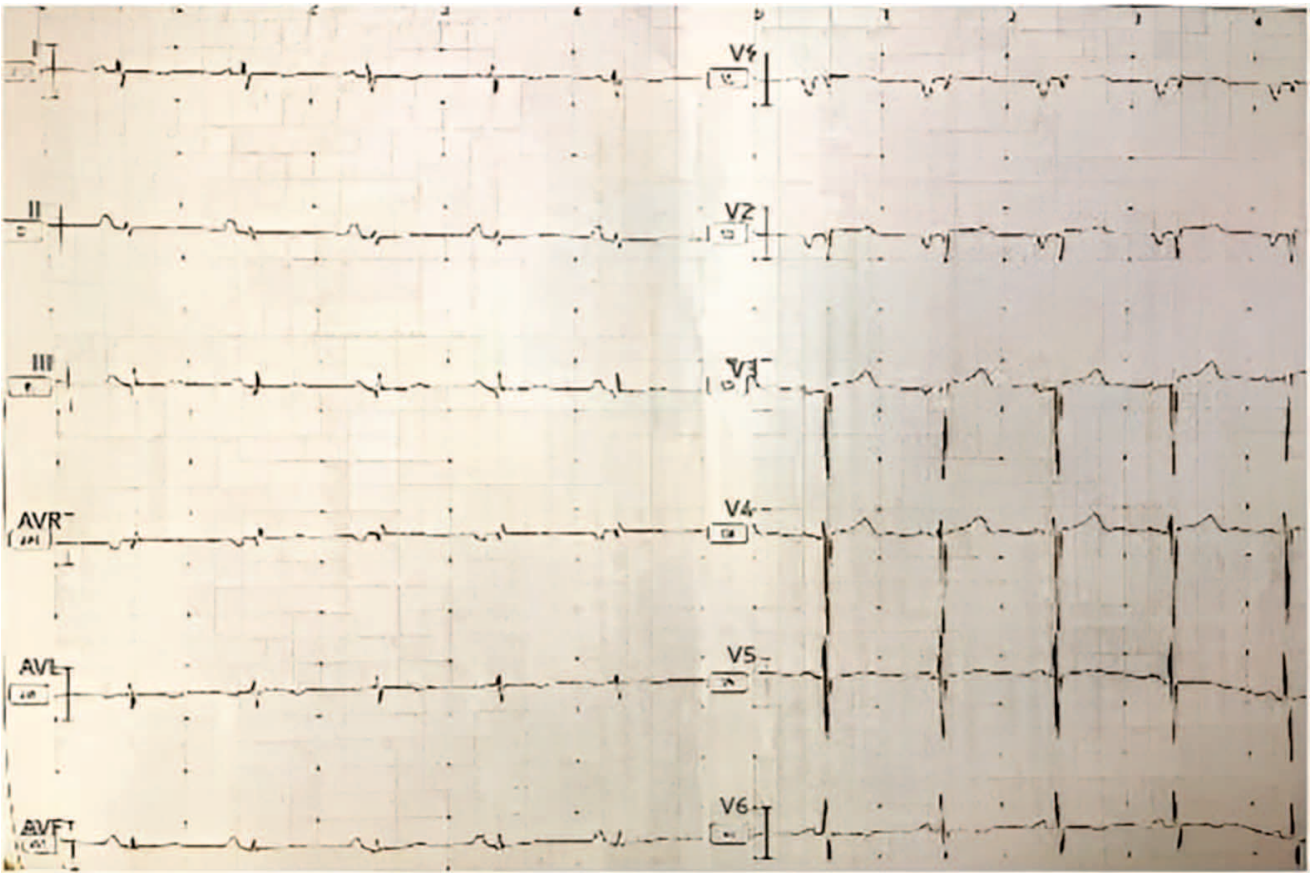


Figure 1. *Electrocardiogram. The ECG showed a low voltage of QRS complexes in extremities leads, and the absence of an adequate increase in the amplitude of the r wave in V1 — V3*

Upon admission to the Cardiology Department, the patient's condition was moderately severe. Body temperature: 36.6° C. Height: 172 cm. Weight: 74.2 kg. Body mass index: 25 kg/m^2.

Upon examination: acrocyanosis, orthopnea, swollen lower limbs up to the middle third of hips. Upon auscultation of the lungs: vesicular respiration reduced in lower sections on both sides with wet, muted stridor. Muffled heart tones. Regular heart rhythm; HR: 76 bpm. AH on both arms: 110/80 mm Hg. The liver protruded 5 cm from the costal margin; the liver is indurated, painless. Bowel and bladder habits: unremarkable.

Complete blood count and urinalysis upon admission: unremarkable. Blood biochemistry: electrolyte disorders: hypochloremia — 95.0 mmol/L (normal value: 98.0–108.0); hyponatremia — 136.0 mmol/L (normal value: 138.0–153.0); increase in creatinine level from 112 μmol/L to 125 μmol/L during hospitalisation (6 days), hypoproteinemia — 62.0 g/L (normal value: 64.0–83.0), increased D-dimer value — 3.63 μg/mL (normal value: 0.00–0.50), albumine — 57.7 % (normal value: 55.8–66.1), ALT — 37.0 U/L (normal value: 3.0–40.0); AST — 45.0 U/L (normal value: 3.0–34.0); BNP — 2,400.6 pg/mL (normal value: 0.0–100.0), cholesterol — 3.82 mmol/L (normal value: 3.50–5.20), triglycerides — 0.81 mmol/L (normal value: 0.50–2.30), LDLP — 2.8 mmol/L (normal value: 0.0–3.30). Coagulation profile: unremarkable.

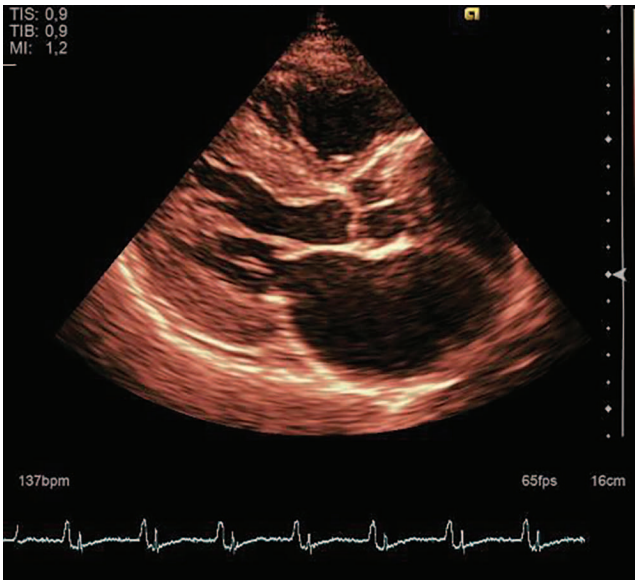
ECG upon admission: sinus rhythm, HR: 84 bpm. Changes in the atrial component with signs of P mitrale. Deviation of the electrical axis of the heart to the right; alpha angle: + 120 degrees. Focal-cicatrical involvement (aneurysm?) of the anterior LV wall, LV myocardium hypertrophy (Fig. 1).

Chest X-ray: bilateral hydrothorax, cardiomegaly, aortic induration, diffuse pulmonary fibrosis. Abdominal ultrasound: diffuse changes in parenchyma, enlarged liver, signs of free fluid in the abdomen. Holter monitoring of ECG: unremarkable.

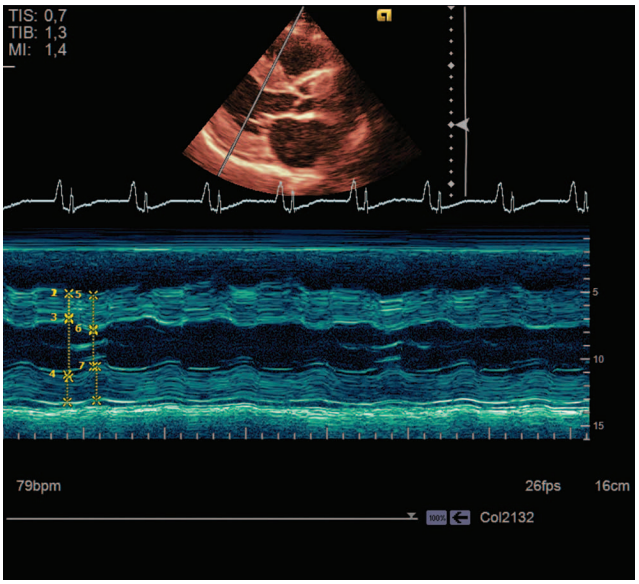
EchoCG (Fig. 2) revealed fluid in pericardial cavity: traces along the posterior wall of up to 0.6 cm (diastole); thickened primary section of the IAA up to 0.6–0.7 cm. Marked symmetric thickening of LV walls: IVS up to 18 mm, LV posterior wall up to 20.6 mm). The LV cavity has smaller size and volume; its global contractility is reduced. No regional contractility abnormalities were found. Restrictive diastolic disorder of LV with

an increased filling pressure (E/Em=16). Dilated cavities of both atria. Mitral regurgitation, grade II. Grade I–II pulmonary hypertension, pulmonary artery systolic pressure (PASYS) 50 mm Hg. Grade II tricuspid regurgitation. LV myocardium contractility: EF moderately reduced — 38 % (Sim[son) (normal value: 54–74 % for women and 52–72 % for men). The EchoCG pattern corresponds to an accumulation disease — heart amyloidosis.

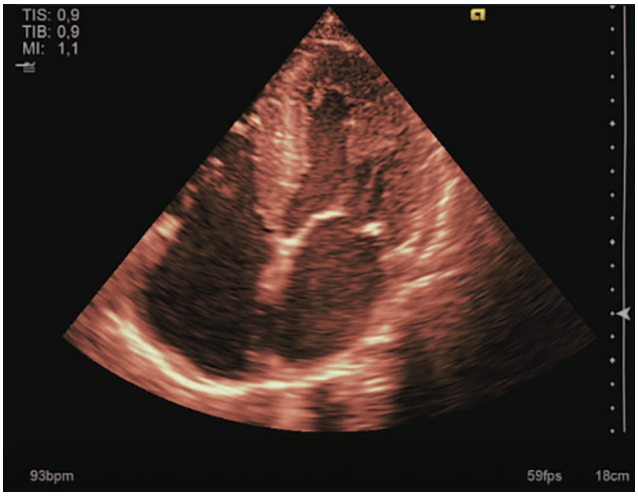
Heart MRI (Fig. 3) shows a typical pattern of heart amyloidosis: diffuse subendocardial contrast agent accumulation in the myocardium of both ventricles without local contractility disorders, thickened myocardium in all segments, pericardial effusion.



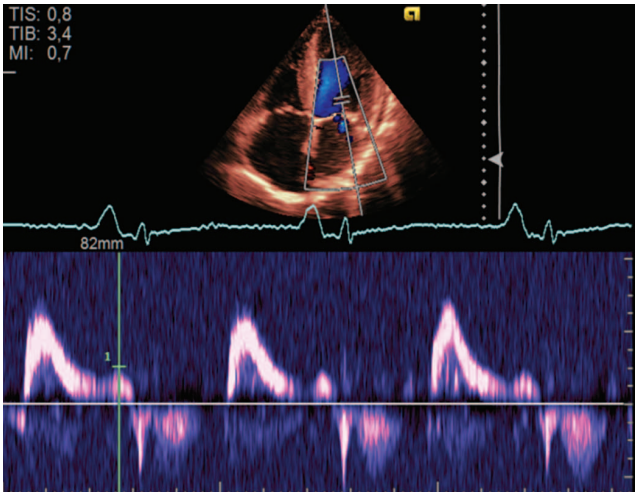
А. *The parasternal position along the long axis, B–mode. A pronounced increase in the thickness of the myocardium, dilation of the LA is visualized. A small amount of fluid in the pericardial cavity*



Б. *The thickening of the IVS and LVPWT in the M–mode, parasternal position along the long axis*

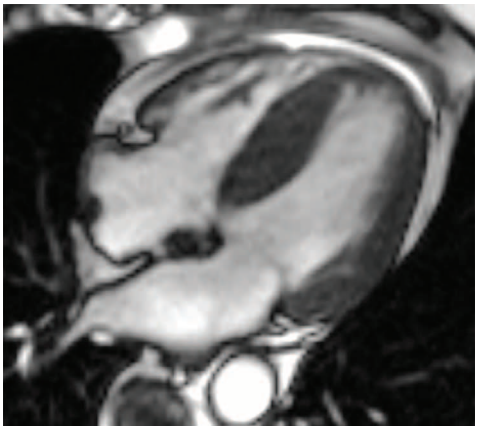


В. *Apical four–chamber position, In B–mode. Pronounced LV myocardial hypertrophy is visualized. Anterosystolic movement of the anterior flap of the mitral valve, atrial dilation*

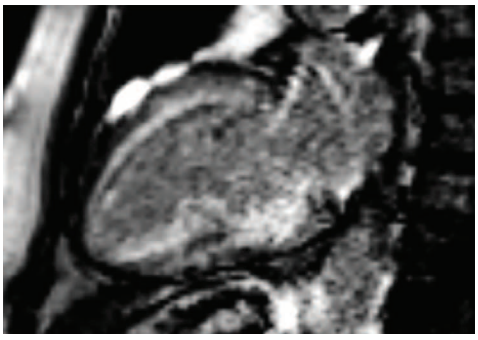


Г. *Restrictive type of DD in the transmittal flow*

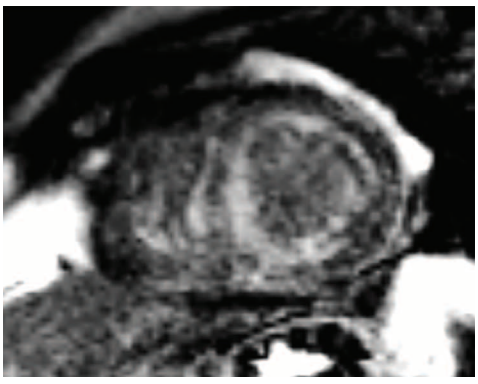
Figure 2. *Echocardiogram*



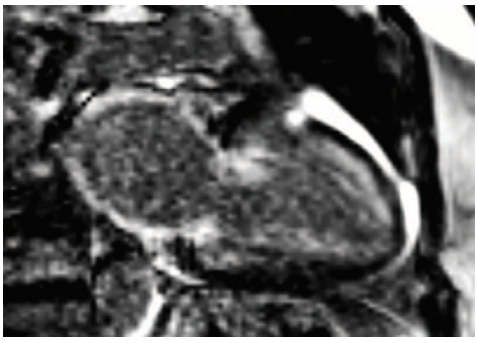
А. *LV myocardial hypertrophy without other heart pathology. Cine–MRI, diastole, precontrast images.*



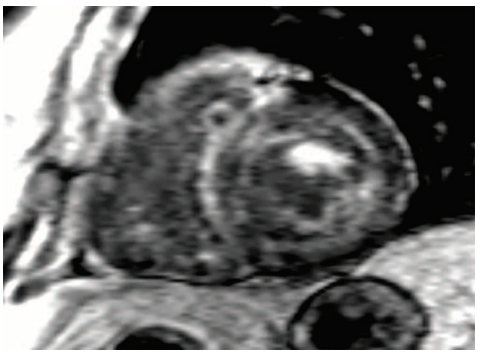
Б. *Diffuse subendocardial enhancement in all segments of the LV myocardium. Late gadolinium enhancement, two chamber view in the LV long axis*



С. *Diffuse subendocardial enhancement in all segments of LV myocardium. Late gadolinium enhancement, LV short axis view*



Г. *LV myocardial hypertrophy, unrelated to other heart pathology. Hypertrophy of the anterior papillary muscle. The technique of cinema — MRI, diastole, without the introduction of a contrast agent*



Д. *MRI technique with delayed phase contrast (LGE). Diffuse subendocardial contrast in all segments of the LV myocardium. Accumulation of contrast agent in the anterior papillary muscle*

Figure 3.

Table 2. Dynamics echocardiography parameters

Index	25.05.2018 at primary EchoCG	04.09.2018	08.02.2019
Left ventricular mass index, g/m^2	189	258,4	333,8
Ejection fraction left ventricular, %	50	50,89	38
Thickness of left ventricular posterior wall, cm	1,9	1,9	2,6
Thickness of the interventricular septum, cm	1,9	1,9	1,82
Left atrium, cm	4,9×6,4	4,42×6,94	4,9
Right atrium, cm	5,0×6,4	4,93×7,19	5,0
Systolic pressure in the pulmonary artery, mmHg	50	45,71	50

The patient underwent subcutaneous adipose tissue biopsy, duodenum submucosa with Congo red staining: no amyloid deposits were found. Planar nuclear scintigraphy in combination with single-photon emission computed tomography was not performed due to technical reasons. Genetic testing did not reveal any mutations in transthyretin gene which cause ATTR–amyloidosis. Sequencing of 10 genes encoding sarcomere myocardial gene showed c.3197C> G (p.Pro1066Arg) mutation in MYBPC3 in heterozygous state, which was previously described in Slavic patients with hypertrophic cardiomyopathy. A test for free lambda and kappa immunoglobulin light chains was not performed due to technical reasons. No cascade family screening for mutation carrier state was performed since the patient did not know anything about his father, his mother died at the age of 75 years old of heart failure; his only son had died in an accident half a year before the patient sought medical assistance.

During the present hospitalisation to the Cardiology Department, the patient had clinical death, but was revived successfully. ECG (after the clinical death): no acute coronary pathology, no changes vs. archive data; troponin — negative. A repeated 24-hour Holter monitoring before and after resuscitation did not reveal any clinically significant rhythm disturbances. No signs of pulmonary embolism were observed during multispiral computed tomography (MSCT) with pulmonary angiography. Brain MSCT did not show any convincing evidence of ischemic changes or skull fractures. For secondary prevention of SCD, a multidisciplinary team decided to implant an implantable cardioverter defibrillator (ICD). In order to rule out amyloidosis and other accumulation diseases with isolated heart involvement, myocardial biopsy was considered.

During hospitalisation, the patient had active diuretic therapy, which helped to achieve subcompensation of HF events; AH was stabilised at 100/70 mm Hg; heart rate was 72 bpm. Taking into account low blood protein, IV albumin infusions were repeated several times. EchoCG showed a rise in the LV myocardium mass index (LVMMI) (Table 2), reduced global LV contractility, cavity dilatation in both atria, and pulmonary hypertension. The final diagnosis upon discharge was as follows:

Primary disease: Non-obstructive hypertrophic cardiomyopathy. Mutation p.Pro1066Arg in MYBPC3.

Complications: Chronic heart failure, grade IIB, NYHA functional class III. Resuscitation for circulatory arrest on February 15, 2019. Cardioverter defibrillator implantation on February 22, 2019.

Comorbidities: Benign prostatic hyperplasia.

After discharge, the patient continued Spironolactone 50 mg in the morning, Torasemide 10 mg at 08.00 am and 10 mg at 02.00 pm, Bisoprolol 2.5 mg, Perindopril 2 mg in the evening (in case of inclination to hypertension it was recommended to skip a dose), Atorvastatin 10 mg/daily.

Despite the therapy, the symptoms of heart failure were worsening fast. On March 25, 2019 (one month after discharge), the patient's wife found him at home lying horizontally without any signs of consciousness and breath. According to medical records, the ambulance was called at 02.08 pm on March 25, 2019. Resuscitation was performed; at 03.27 pm, the patient was pronounced dead. According to the wife, no postmortem study was conducted, as she had refused. An official request was sent to the polyclinic at the patient's place of residence in order to obtain information on postmortem examination and its results. Pursuant to Federal Law of the Russian Federation No. 152–FZ, On Personal Information, the polyclinic refused to provide any information.

Discussion

Differential diagnosis of genetically caused HCM and amyloid cardiomyopathy is challenging due to similar clinical manifestations and imaging data.

In the case study, the only cardiac manifestations were increased LV wall thickness, pericardial effusion, long-lasting HFpEFCH, and no response to conventional CHF therapy (ACE inhibitors, beta-blockers), low voltage of QRS complexes, pseudoinfarction changes, mass-voltage dissociation. He did not have any extracardiac manifestations. The level of wtATTR–CMP suspicion was 2, the modelled probability was 3 % (EstimATTR). Besides, the myocardium thickness was 26 mm, which necessitated the search for other causes of LVH, despite a history of AH. In this case study, the MRI pattern of the patient with marked myocardium hypertrophy was attributed to amyloid cardiomyopathy. However, extracardiac biopsy did not confirm amyloidosis; genetic testing did not reveal transthyretin gene mutations causing ATTR–amyloidosis. Isolated amyloid myocardial involvement could

have been ruled out if endocardiac biopsy had been performed, which was impossible to the severe condition of the patient. Unfortunately, postmortem examination was not performed and did not rule out the amyloid origin of cardiomyopathy. Taking into account genetic mutations, contrast accumulation in MRI should be interpreted as HCM-caused fibrosis. It appears that up to the age of 59 years old this patient had asymptomatic HCM, then HCM was associated with marked signs of CHF.

In this case, the cardiac arrest was probably caused by asystole due to HF progression; if this patient had ventricular fibrillation or ventricular tachycardia, ICD would have been triggered and would have prevented the patient's death.

There are also literature references of challenging differential diagnosis of HCM and amyloid cardiomyopathy. A 64-year-old woman presented with chest pain and progressive shortness of breath. EchoCG and MRI results assumed HCM. The patient did not have any family history of this disease, however, her father suddenly died at the age of 48 years old. The grandfather and two paternal uncles died before they were 40 years old from an unknown cause.

Genetic testing did not reveal any significant mutations, unlike the case study in question. One year later, the patient underwent a re-examination, where ECG showed low voltage and EchoCG revealed severe diastolic dysfunction. A repeated MRI showed abnormal late subendocardial gadolinium enhancement, similar to the case study in question. Based on the results, adipose tissue biopsy was performed, but the results were negative. Endocardiac biopsy was positive for amyloidosis. The article does not describe the type of amyloidosis [13].

Conclusion

Challenges with differential diagnosis of HCM and amyloid cardiomyopathy are due to similar clinical manifestations, instrumental data, use of insufficiently sensitive diagnostic tests. Heart amyloidosis is a rare disease, which affects the efficiency of disease detection. Despite the fact that both diseases are mostly similar to CHF, timely differential diagnosis is essential for the adequate management and prognosis for the patient.

The co-existence of genetically caused hypertrophic cardiomyopathy and amyloid heart involvement cannot be ruled out.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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