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ЛЕТАЛЬНЫЙ КЛИНИЧЕСКИЙ СЛУЧАЙ АМИЛОИДНОЙ КАРДИОМИОПАТИИ У ПОЖИЛОЙ ПАЦИЕНТКИ

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Amyloid Cardiomyopathy: Review of A Fatal Case Report

Резюме

Пристальное внимание к проблеме амилоидной кардиомиопатии в последние годы обусловлено значительным приростом выявляемости заболевания на фоне повышения чувствительности и специфичности методов визуализации, применяемых в кардиологической практике, наряду с появлением новых перспективных методов диагностики и специфической терапии Выбор тактики лечения системного амилоидоза напрямую зависит от результатов типирования амилоидогенных белков, которое стало возможным благодаря развитию протеомики, основанной на масс-спектрометрии. На сегодняшний день доказано, что важной и часто недиагностированной причиной хронической сердечной недостаточности и нарушений сердечного ритма, особенно в пожилом возрасте, является амилоидная кардиомиопатия. Существует более 15 типов белков-предшественников, способных вызывать системный амилоидоз, однако только 2 из них накапливаются в интерстиции сердца: легкие цепи клонального иммуноглобулина (AL) и тетрамерный белок транстиретин (TTR). О значительной распространенности генетического транстиретинового амилоидоза дикого типа (ATTRwt), ранее именуемого старческим системным амилоидозом, говорят следующие цифры: у 13 % пациентов, госпитализированных по поводу декомпенсации хронической сердечной недостаточности с сохранной фракцией выброса левого желудочка диагностической находкой явилась транстиретиновая амилоидная кардиомиопатия, среди пациентов старше 80 лет данная патология post mortem выявляется в 20-25 % патологоанатомических заключений, и в 37 % случаев в группе долгожителей (пациентов старше 97 лет). Даже при ранней диагностике ATTR-амилоидоза продолжительность жизни от момента появления первых симптомов составляет 10-12 лет, так как заболевание необратимо прогрессирует, приводит к инвалидности вследствие тяжелого поражения сердца и полинейропатии. Поздняя же диагностика системного амилоидоза обусловлена низкой осведомленностью врачей первичного звена, наличием коморбидности у пожилых пациентов, отсутствием специфических симптомов заболевания и доступных диагностических скрининг-методов, и предопределяет неблагоприятный прогноз данного заболевания, особенно при формировании амилоидной кардиомиопатии.

Нами представлено описание клинического случая пожилой пациентки с торпидным течением прогрессирующей декомпенсированной застойной сердечной недостаточности, окончившейся летально на 3-и сутки госпитализации. Прижизненная верификация транстиретиновой амилоидоидной кардиомиопатии не представлялась возможной. Эхокардиографические критерии приблизили нас к диагнозу, а патологоанатомические исследования позволили подтвердить диагноз системного амилоидоза с преимущественным поражением сердца.

Ключевые слова: *системный амилоидоз, амилоидная кардиомиопатия, сердечная недостаточность, сердечно-сосудистые заболевания, клинический случай*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Информированное согласие не требуется в силу невозможности идентифицировать пациента

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Abstract

Close attention to the problem of amyloid cardiomyopathy in recent years has been caused by a significant increase in the disease detection simultaneously with increased sensitivity and specificity of imaging methods used in cardiological practice, along with the emergence of new promising diagnostic methods and specific therapy. The choice of treatment tactics for systemic amyloidosis directly depends on the results of typing of amyloidogenic proteins, which became possible due to the development of proteomics based on mass spectrometry. To date, it has been proven that amyloid cardiomyopathy is an important and often undiagnosed cause of chronic heart failure and cardiac arrhythmias, especially in the elderly. There are more than 15 types of precursor proteins capable of causing systemic amyloidosis, but only 2 of them accumulate in the interstitium of the heart: light chains of clonal immunoglobulin (AL) and tetrameric protein transthyretin (TTR). The significant prevalence of wild-type genetic transthyretin amyloidosis (ATTRwt), formerly referred to as senile systemic amyloidosis, is indicated by the following figures: in 13 % of patients hospitalized for decompensation of chronic heart failure with preserved left ventricular ejection fraction, transthyretin amyloid cardiomyopathy was a diagnostic finding, among patients over 80 years of age, this pathology is detected post mortem in 20-25 % of pathoanatomic reports, and in 37 % of cases in the long-lived group (patients over 97 years of age). Even with early diagnosis of ATTR-amyloidosis, the life expectancy from the moment the first symptoms appear is 10-12 years, as the disease progresses irreversibly, leading to disability due to severe heart damage and polyneuropathy. The late diagnosis of systemic amyloidosis is due to the low awareness of primary care physicians, the presence of comorbidity in elderly patients, the absence of specific symptoms of the disease and available diagnostic screening methods, and determines an unfavorable prognosis of this disease, especially with the formation of amyloid cardiomyopathy. The relevance of this topic is due to the need to improve diagnostic algorithms and reduce the time for primary diagnosis of amyloid cardiomyopathy in order to improve the prognosis of the disease.

We have described a clinical case of an elderly patient with a torpid course of progressive decompensation of congestive heart failure, which ended fatally on the 3rd day of hospitalization. Echocardiographic criteria brought us closer to the diagnosis of amyloid cardiomyopathy, but pathoanatomic studies have confirmed the diagnosis of systemic amyloidosis with predominant heart damage.

Key words: *systemic amyloidosis, amyloid cardiomyopathy, heart failure, cardiovascular diseases, clinical case*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

Informed consent is not required due to the impossibility of identifying the patient

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AL — amyloidosis light chain, ATTRwt — amyloidosis transtyretin wild type, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, NYHA — New York Heart Association, SpO2 — peripheral oxygen saturation, TTR — transthyretin, AVO — atrioventricular opening, BP — blood pressure, AC — amyloid cardiomyopathy, BMI — body mass index, LVEDD — left ventricle end-diastolic dimension, LVEDV — left ventricular end-diastolic volume, COI — cutoff index, LVESD — left ventricle end-systolic dimension, chest CT — computed tomography of thoracic organs, LV — left ventricle, LA — left atrium, IVS — interventricular septum, IU — international units, MSCT — multispiral computed tomography, MRI — magnetic resonance tomography, ICU — intensive care unit, RV — right ventricle, RA — right atrium, PCR — polymerase chain reaction, PET — positron emission tomography, CF — cardiac failure, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, LVWT — left ventricular wall thickness, EF — ejection fraction, FC — functional class, daily monitoring of ECG — 24-hour Holter monitoring, CCFwLVEF — chronic heart failure with preserved left ventricle ejection fraction, CDH — central district hospital, RR — respiratory rate, HR — heart rate, ECG — electrocardiography, EMB — endomyocardial biopsy, ECA — cardiac electrical axis, echoCG — echocardiography

Introduction

Amyloidosis is a multisystem disease, associated with depositions of insoluble amyloid fibrils containing incorrectly aggregated proteins, in the extracellular space. Each type of amyloidosis has its own type of amyloidogenic precursor protein, the name of which underpins the modern classification of the disease [1]. It has been proven that amyloid cardiomyopathy (AC) significantly worsens disease prognosis, and in 98 % of cases it develops in primary systemic amyloidosis, such as AL-amyloidosis caused by deposition of immunoglobulin light chain (AL), and TTR-amyloidosis (ATTR), where transthyretin tetramers are deposited (ATTR) [2]. Interstitial infiltration of amyloid in the heart impacts restrictive cardiomyopathy phenotype on the pathogenic level and causes myocardial diastolic and (later) systolic dysfunction. Cardiac remodelling and amyloid deposition in the heart walls can lead to heart rhythm and conductivity disorders. In elderly patients, reduced quality of life can be a result not only of the age, but also of non-specific symptoms of AC due to ATTRwt, which vary from minimal to the symptoms of progressive decompensated cardiac failure (CF). Therefore, routine examination is not sufficient for diagnosis verification. The peculiarities of AC diagnosis lie in identification of suspicious clinical signs, associated with amyloidosis phenotype, and suspicion verification using imaging and specific disease-identifying laboratory tests [3]. Given the absence of specific signs and symptoms of this disease, as well as availability of sensitive diagnostic methods, such as heart MRI and scintigraphy, endomyocardial biopsy (EMB) with subsequent amyloidogenic

protein typing using immunohistological and biochemical assays, early diagnosis and timely initiation of disease-specific therapy is a topical problem in the real-time clinical practice. The incidence of AC, low rates of early diagnosis verification and, as a result, lack of ability to timely initiate disease-specific therapy, lay behind the importance of a detailed discussion of a lethal case study of amyloid cardiomyopathy in an elderly female patient.

Clinical case study

On 02/09/2024 *Patient M, a 75-year-old female patient,* was urgently admitted to the intensive care unit (ICU) of N. A. Semashko Republican Clinical Cardiological Dispensary in Simpheropol in serious condition; the severity of her condition was caused by cardiopulmonary failure and generalised oedema syndrome. Upon admission, the patient complained of marked weakness, heart problems, shortness of breath after minor physical activities (walking for 5–10 minutes), swollen ankles, abdomen dilatation. The patient noted weight loss of over 10 % over the past six months.

Past medical history: according to the patient, she got ill in February 2024, when she noted arrhythmia, but she did not seek medical advice. In June, after the patient returned from health resort treatment, her condition deteriorated: shortness of breath and lower limb swelling developed, and in June the patient was admitted to the internal medicine ward at the central district hospital at the place of the patient's residence. Chest CT dated 30/07/2024 showed right pneumohydrothorax, compensated right atelectasis, cardiomegaly, pulmonary engorgement, ascites. Pleural puncture was performed: pleural fluid examination showed serous transudate with the relative density of 1,010 g/mL, protein: 19 g/L; microscopic findings: mesothelium — 5–6 per HPF, lymphocytes — 3–4 per HPF, RBC — 10–12 per HPF, no atypical cells. She received symptomatic treatment and was discharged without any improvements. Because of persistent signs of congestive CF, one month later, the patient was hospitalised to the geriatric ward of the Crimean Republican Clinical Hospital for War Veterans with the following diagnosis: CCF, stage 2B; senile asthenia. EchoCG dated 07/08/2024 showed dilated right heart and left atrium, impaired diastolic myocardial function, EF 50 %; valves: unremarkable. Repeated chest CT dated 08/08/2024 confirmed cardiomegaly, bilateral hydrothorax and signs of pulmonary engorgement: right pleural space — free fluid (density: approx. 8 HU), layer thickness: up to 48 mm; left cavity: free fluid (density: approx. 5 HU), layer thickness: up 9 mm. Abdomen CT dated 08/08/2024: ascites, hydrosarca, fatty hepatosis.The therapy included treatment of CCF symptoms (furosemide 100 mg/day, verospiron 50 mg/day, metoprolol 50 mg/day, candesartan 32 mg/day), steroids (dexamethasone 8 mg/day), lipid-lowering drugs (rosuvastatin 5 mg/day). The patient was discharged without improvement. At the place of residence, the patient had follow-up chest X-ray examination (29/08/2024): the horizontal fluid level on the right is at the level of the IV rib, left pleural diaphragmal corner is free. Since there were no any positive changes in her condition, the patient had to visit the outpatient clinic at the cardiac dispensary, where she was ungently hospitalised.

Physical examination: severe general condition, lucid; body temperature: 36.4 °C, BMI = 18; by auscultation: above the lungs, the respiration is harsh, weaker in side areas, and absent in lower sections; no rales; respiratory rate is 24/min; oxygen saturation (SpO2) 96 %; muffled, arrhythmic cardiac tones, no heart murmurs; HR 60 bpm, arrhythmical pulse of poor volume, BP 85/55 mm Hg; symmetrical lower limb oedema up to the upper third of shin; abdomen soft on palpation, enlarged because free fluid, positive fluctuation symptom. Complete blood count showed no abnormal results: Hb 133 g/L, RBC 4.43×10^{12}/L, platelets 175×10^{9}/L, WBC 8.6×10^{9}/L, ESR 20 mm/h. Blood biochemistry: glucose 4.9 mmol/L, cholesterol 3.8 mmol/L, bilirubin 14.7 mmol/L, urea 23.0 mmol/L, creatinine 197 mmol/L, total protein 57 g/L, albumin 30 g/L, ALT 32.9 U, AST 24.7 U, potassium 4.9 mmol/L, sodium 129.3 mmol/L, calcium 1.27 mmol/L. Coagulation profile: prothrombin time 25.0, PTI 41.2 %, INR 2.0, fibrinogen A 4.5 g/L, APPT 41 s, thrombin clotting time 21 s. Cardiac markers: myoglobin — 72.0 ng/mL (normal range: < 70 ng/mL), troponin I — 0.14 ng/mL (normal range: < 0.01 ng/mL), NT-proBNP — 9,086 pg/mL. Markers of viral hepatites, HIV, syphilis: negative. Urinalysis results show proteinuria 0.12 g/L, leukocyturia — 10 per HPF. ECG upon admission (Figure 1): normal voltage; atrial flutter with AV conduction; HR 108 bpm, electrical cardiac axis is of normal position, left ventricle hypertrophy.

Transthoracic echoCG (Figure 2) dated 04/09/2024: LA 4.6 cm, LVEDD 3.6 cm, LVESD 3.0 cm, LVEDV index 46 mL/m^2, LVPWT 1.3 cm, IVST 1.3 cm, LVEF 36 %, RV 2.9 cm; moderately dilated right ventricle and both atria; normal LV dimension and volume; valves — unremarkable; moderate concentric LV myocardial hypertrophy; echo-structure of LV myocardium looks finely grained and shiny with typical glow; marked relative tricuspid insufficiency; moderate pulmonary hypertension with systolic pulmonary pressure of up to 42 mm Hg; significantly lower contractility of LV myocardium; significantly impaired diastolic function; right pleural cavity with signs of up to 600 mL of free fluid; no free fluid in pericardial cavity and left pleural cavity. Longitudinal deformity of the left ventricle was not accessed due to unavailability of technical capacities.

Clinical examination results were used to verify the primary diagnosis: primary amyloidosis with predominant cardiac involvement, complicated by stage 2B CCF with reduced myocardial contractility (EF 36 %), functional class 4 (NYHA); persistent atrial

fluttering (CHA2DS2-VASc 4 points, HAS-BLED 1 point, EHRA 2b); right-sided hydrothorax, ascites. The patient had therapy complying with clinical guidelines and medical assistance standards for her congestive heart failure, including cardiotropic (a combination of valsartan + sacubitril, bisoprolol), dehydration (furosemide, spironolactone), antiarrhythmic (amiodarone), anticoagulation (rivaroxaban) therapy and SGLT2 inhibitors (dapagliflozin) (standard doses). EMB was planned to histologically confirm the type of systemic amyloidosis.

Due to the antiarrhythmic therapy, on day 2 of hospitalisation the patient had sinus rhythm (Figure 3); however, the patient's condition remained the same (critical but stable). Despite the combined diuretic therapy (furosemide 100 mg intravenous drip and oral spironolactone 100 mg), no positive diuresis was observed, and hydrosarca persisted.

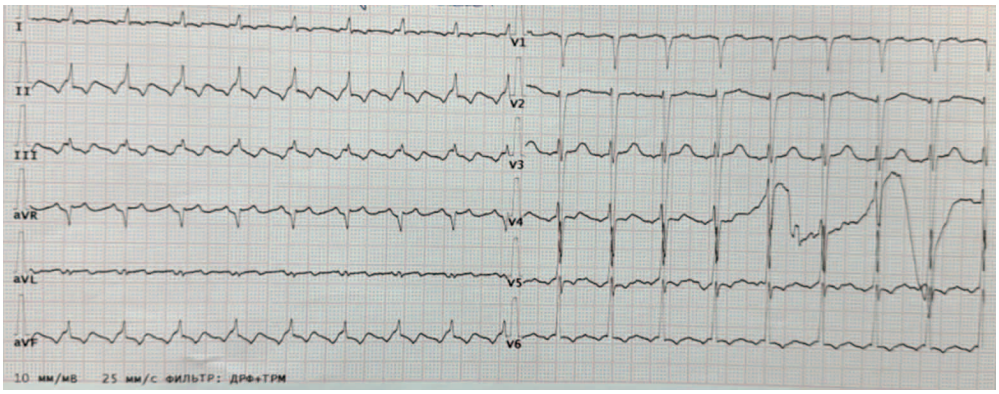

Figure 1. *ECG on admission — Atrial flutter*

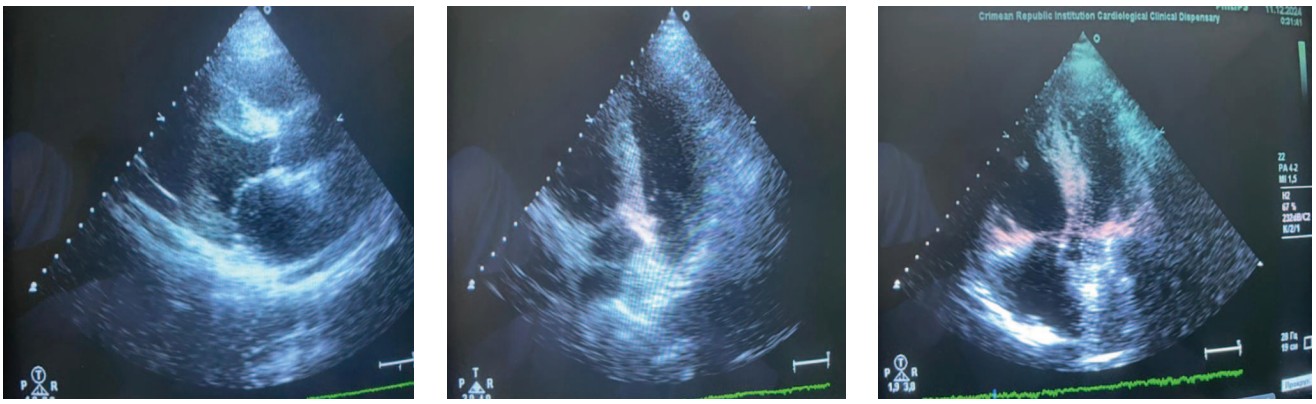

Рисунок 2. *Характерное для амилоидной кардиомиопатии «свечение» при трансторакальной ЭхоКГ*
Примечание. А — парастернальная позиция по длинной оси; Б и В — верхушечная позиция по длинной оси
Figure 2. *Amyloid cardiomyopathy "glow" during transthoracic echocardiography findings*
Note. A — parasternal position along the long axis; Б, B — apical position along the long axis

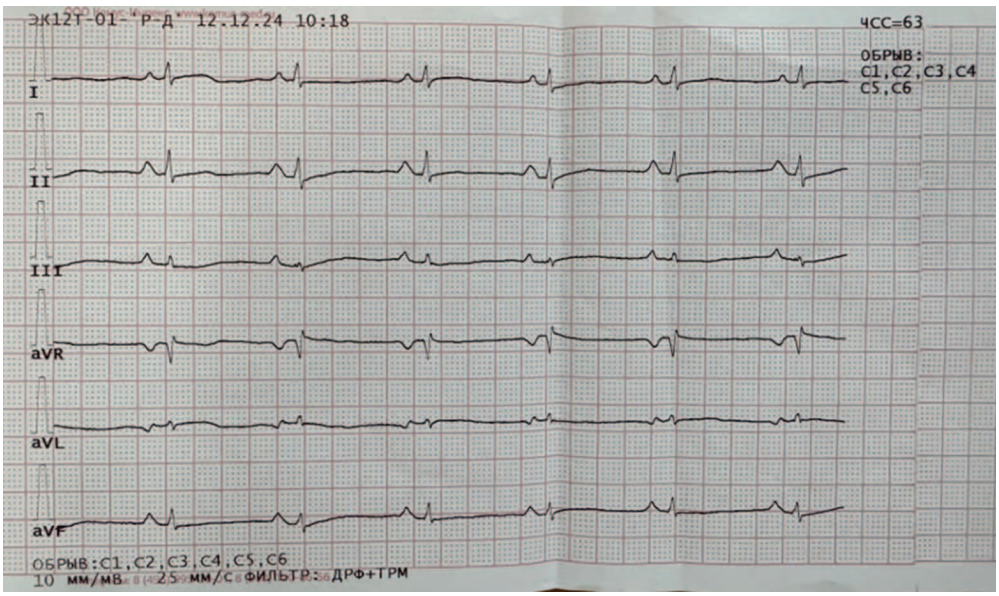

Figure 3. *ECG on the second day of hospitalization — sinus rhythm restoring after pharmacological cardioversion*

On day 3 of hospitalisation, the patient's condition deteriorated: she suddenly lost consciousness, unassisted breathing was ineffective, and resuscitation was initiated. Despite the intensive care, the patient went into cardiac arrest, monitors showed asystole, and the patient was pronounced clinically dead. Cardiac compressions, tracheal intubation, breathing support with a breathing bag and intravenous adrenaline were ineffective, and in 30 minutes, the natural death was pronounced.

Autopsy Results

A yellow clear fluid was found: in abdomen — 1,000 mL, in right pleural cavities — 2,000 mL, in left pleural cavities — 1,000 mL, in pericardial cavity — 100 mL. Heart: 700 g, 14×11×7 cm, with rounded apex, formed by LV; enlarged cardiac cavities, right atrioventricular opening (AVO) perimeter: 12 cm, left AVO: 10 cm, aorta: 7 cm. The myocardium is of cartilaginous density, light-brown in colour, shiny; LV wall thickness in the cross-section 1.0 cm from the fibrous atrioventricular ring 1.8 cm, RV — up to 0.5 cm. Coronary arteries are rigid, with single dense greyish-yellow plaques covering up to 50 % of intima surface, the opening is 50 % occluded. The lungs are pushed forwards by the fluid; dense, a lot of foamy liquid and thin blood drop from the cur surface.

Histological examination

Heart: positive staining with Congo red for amyloid and positive green glow in polarised light; uneven vascular congestion, thickening and amyloidosis of small and medium-sized vessel walls; perivascular, intermuscular foci of amorphous eosinophilic amyloid masses; thinning, atrophy and tortuosity of muscle fibres; dystrophy and moderate hypertrophy of cardiac myocytes; focal fragmentation of muscle fibres.

Brain: perivascular, pericellular oedema; glial cell dystrophy, areas of brain tissue rarefication; vascular congestion.

Lungs: poor blood supply to vessels; thickened interalveolar septa with eosinophilic amyloid deposits; the same deposits are observed along the vessels.

Liver: preserved frame structure; vast amyloid deposits in vessel walls, along portal tracts; dystrophic hepatic cells, oedema.

Kidneys: thickened, sclerotic glomerule capsule and vascular walls, amyloid deposits. Parenchyma with focal lymphocytic and globo-cellular infiltration, sclerosis and hyaline degeneration; vast areas of amyloid deposits along the vessels. Areas of amyloid deposits along the vessels are observed also in the pancreas.

The autopsy results show that the death was caused by progressive cardiopulmonary failure, namely pulmonary and brain oedema, resulting from the primary disease: primary systemic amyloidosis with predominant cardiac involvement.

Discussion

Numerous recent studies show undervaluation of ATTR amyloidosis as a cause of arrhythmias and impaired contractility, as well as progressive CF in elderly patients [4], which was observed in this clinical case study. The diagnostic search for the causes of torpid decompensated CCF and atrial fluttering was limited to ischaemic heart disease, acquired valvular problems and amyloid cardiomyopathy. The medical history of the patient did not show any data on arterial hypertension, chronic or acute forms of ischaemic heart disease, including myocardial infarction, or valvular heart disease, which could cause progressive CCF, that is why AC was most probably. According to the current idea, wild type ATTR (ATTR-wt) is associated with generalised amyloid deposits in interstitial tissue of parenchymal organs because of age-related defects of transthyretin tetramers secretion by the liver [5], and it can bring about the mentioned cardiac signs and symproms. Also, a typical clinical sign of AC was observed: reduced QRS voltage seen on ECG and mismatch between ECG results of myocardial hypertrophy and echoCG observations, i.e., reduced ECG/echoCG index below 7.8; sensitivity and accuracy of this sign are 94 % and 82 %, respectively, while its negative predictive value — 97 % [6]. A minor increase in cardiac markers (myoglobin — 72.0 ng/mL, troponin I — 0.14 ng/mL) ruled out massive myocardial damage, while an excessively high NT-proBNP level (9,086 pg/mL) suggested severe myocardial dysfunction from other causes. A combination of cardiac manifestations, such as weakness, arrhythmia, severe drug-resistant decompensated CCF (hydrosarca). ECG signs and echoCG observations: dilated right heart and LV, concentric LV myocardial hypertrophy (LV wall thickness up to 1.3 cm), diastolic and myocardial dysfunction (EF 36 %), and pathognomonic fine-grained structure of LV myocardium with glow confirmed AC. The only thing left to do was to identify the type of amyloidosis. The key differential diagnosis was to confirm ATTR- or AL type of systemic amyloidosis, which have similar manifestations, observed in this patient, namely she was over 70 years of age, lost weight and had symptoms of torpid progressive CCF. In this case study, where the patient did not have any extracardiac manifestations, the hypothesis of ATTRwt phenotype was supported only by arrhythmia (atrial flutter) [7]; studies show that the incidence atrial fibrillation/flutter in patients with AC in ATTR-wt was higher (71 % of patients) than in AL amyloidosis (26 %) [8]. Minimal proteinuria (0.12 g/L) did not help reliably differentiate between ATTR- and AL-amyloidosis, although, the latter is more often associated with nephrotic levels of proteinuria. Unfortunately, we did not have a chance to perform planned intravital identification of the type of systemic amyloidosis: subcutaneous tissue biopsy and EMB with subsequent identification of amyloid protein type, tests for plasma cell dyscrasia (bone marrow biopsy

with cytofluorometry, analysis of released paraproteins: immunofixation and electrophoresis of serum and urine proteins with quantification of monoclonal and polyclonal immunoglobulins). Even postmortem, it was impossible to verify systemic ATTR amyloidosis using routine autopsy methods, since no immunohistological and biochemical amyloid analysis was performed [9]. According to the literature, symptoms of CCF are a predictor of poor outcome in patients with systemic amyloidosis, because, if untreated, the mean survival rate is approximately one year, and half a year if symptoms of severe CCF are present [10]. This fact was confirmed in this clinical case study: six months after the onset of first cardiac symptoms (arrhythmia) and three months after CCF symptoms, the patient died of torpid CCF progression. Independent risk factors of poorer survival rates in AC from ATTR are also age, NYHA FC III–IV, systolic BP < 100 mm Hg, resistance to diuretics, while NT-proBNP levels ≥ 1,800 ng/L increase the all-cause death rates [11]. It is worth noting that all mentioned risk factors of poor outcome were observed in this case study, which made the patient's prognosis even worse. The mismatch between LV wall thickness on ecoCG (1.3 cm) and autopsy (1.8 cm) observed in this patient is rather a pattern than an exclusion. According to the literature, the diagnostic efficiency of intravital identification of LV hypertrophy at postmortem measurement was low: the difference between autopsy and echoCG results for LV wall thickness was 3.3 to 5.2 mm, and for IVS — from 1.3 to 1.4 mm. This phenomenon can be caused by postmortem changes in the heart, which should be taken into consideration when diagnosing heart pathologies [12]. Unfortunately, despite numerous hospitalisations, neither healthcare professionals at the sanatorium, nor at the CDH, nor at the republican hospitals were able to suspect systemic amyloidosis, which, in our opinion, is a sign of their poor awareness. Early and prompt diagnosis of AC where amyloidosis is suspected is the top priority and a key to efficient therapy, since early therapy initiation can prevent further deposition of amyloid and progressive damage to target organs [1, 3]. Up to 2018, the only possible therapy of AC at ATTR was heart transplantation, the availability of which was significantly limited due to elderly age of patients and the need to transplant several organs (heart and liver). A breakthrough in the ATTR therapy was recently introduced and approved drug therapies, based on TTR gene inhibition (TTR protein synthesis inhibition), or TTR stabilisation (prevention of TTR tetramers dissociation to fibrils) [13].

In this case, the right moment was lost, and even despite the scientific breakthrough in the management of such patients with specific therapies [14], the patient was fated to die. Two days of hospitalisation after AC diagnosis was made did not make it possible to identify the type of amyloid while the patient was alive, and initiate specific therapy.

Conclusions

This clinical case emphasises the need for raising awareness of primary care providers about systemic amyloidosis in elderly patients, its diagnostic criteria and possible use of disease-specific therapy. Patients with AC need personalised diagnostic and therapeutic approach by a multidiscipline team of healthcare providers to develop a therapeutic strategy and access the potential role of available therapies to manage CF. Due to significant achievements in modern healthcare for the management of this category of patients, timely diagnosis will help in prompt therapeutic interventions to improve survival rates, physical functioning and/or quality of patients' life.

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Author Contribution:

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

Soldatova O.V.: manuscript editing, drafting articles, approval of the final status of articles, interpretation clinical case data, search of references

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