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Case Report

Unveiling the complexity of cardiac amyloidosis: a comprehensive case report

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ABSTRACT

This case report documents a woman in her sixties who initially presented with cardiac symptoms such as heart palpitations, shortness of breath, and fluctuating blood pressure. Following her hospital admission, she received a diagnosis of paroxysmal atrial fibrillation and underwent successful electrical cardioversion. Despite this intervention, her symptoms persisted, necessitating radiofrequency ablation of the Cavo-tricuspid isthmus, which proved to be highly effective. Subsequent diagnostic testing revealed the presence of coronary artery disease, atherosclerotic cardiosclerosis, and mitral valve abnormalities, all of which were managed appropriately. Upon discharge, the patient was prescribed a medication regimen comprising anticoagulants, hypotensive therapy, and statins, which she tolerated well. However, her symptoms deteriorated, leading to a referral to a specialized center where she was promptly diagnosed with cardiac amyloidosis (CA) and received appropriate treatment. Adjustments to her treatment plan were made based on this diagnosis, and a cardiac MRI confirmed the presence of amyloidosis. A biopsy of the buccal mucosa further confirmed the presence of AL-amyloidosis based on immunohistochemistry test results. The patient commenced chemotherapy, which unfortunately led to kidney damage but ultimately resulted in significant improvement in her condition. Recurrent atrial fibrillation episodes necessitated further interventions, which were performed swiftly and effectively. Multi-organ assessments revealed numerous abnormalities, guiding tailored management strategies. A multidisciplinary team comprising cardiology, hematology, and general practice specialists coordinated the patient's care, focusing on pharmacotherapy and lifestyle modifications, which were found to be highly effective. Emphasis was placed on continuous monitoring and adherence to treatment plans for long-term management, resulting in positive outcomes.

Keywords: CA, Paroxysmal atrial fibrillation, Radiofrequency ablation, AL-amyloidosis, Chemotherapy-induced kidney damage, Recurrent atrial fibrillation

INTRODUCTION

Amyloidosis is a disease where misfolded proteins accumulate in the body, leading to the formation of amyloid fibrils that can cause specific diseases affecting different organs, including the heart. It is important to detect cardiac involvement as it significantly impacts disease prognosis. CA is a common subtype of amyloidosis that can lead to restrictive cardiomyopathy, and there are two main subtypes of CA: AL and ATTR.[1-3]

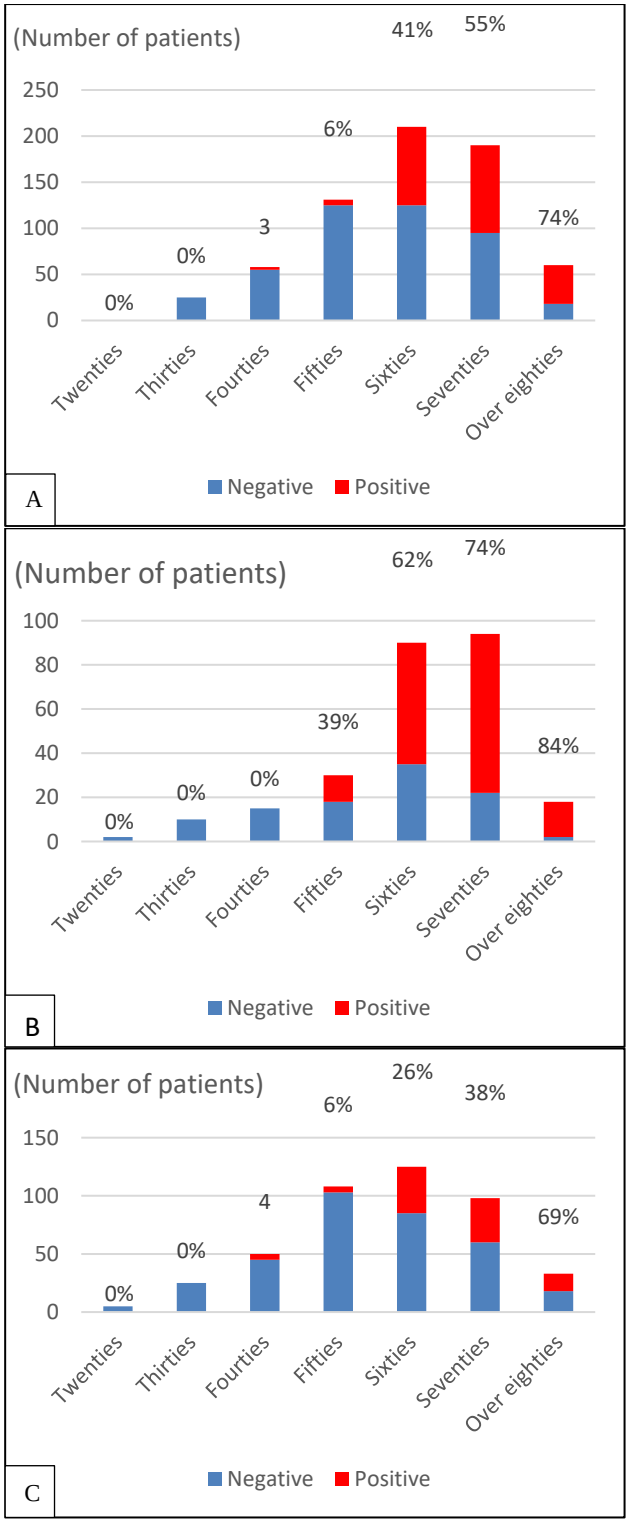

Figure 1 (A-C): Amyloid-positive rate in each age group in the overall cohort, men, and women the rate increased with age and men had a higher amyloid-positive rate than women.[4]

CTS is considered a "red flag" for CA, but there is no precedent of amyloid deposition in the removed tenosynovium. Therefore, it is crucial to select patients with a high likelihood of CA to prevent unnecessary pathological inspection.[4]

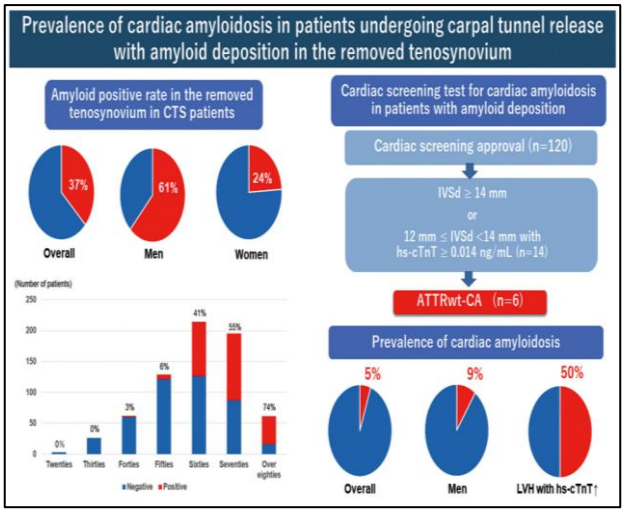

Figure 2: Prevalence of CA.[4]

TTR-CA is more prevalent in men than in women within the AS population. The presence of carpal tunnel syndrome, lumbar spinal stenosis, deafness, premature pacemaker implantation, disproportionate heart failure symptoms despite non-severe AS, right ventricular failure, and the absence of macroglossia and soft-tissue manifestations suggest TTR-CA.[5]

Cardiovascular amyloidosis is a myocardial disease marked by extracellular amyloid infiltration throughout the heart. This condition is associated with immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis. The infiltrative process leads to biventricular wall thickening with low cardiac output and atrial dilatation. Intramyocardial vessels are often affected, causing decreased myocardial perfusion. The conduction systems are also often affected, with atrial arrhythmias, atrioventricular conduction delays, and ventricular arrhythmias being common.[1]

CA or "stiff heart syndrome" is a condition where amyloid proteins infiltrate the cardiac walls, increasing wall thickness and ventricular stiffness. It affects other organs too. Diagnosis and treatment are challenging as symptoms may appear only at later stages. Awareness and knowledge are crucial for effective management.[6]

It can affect arterioles, causing angina or myocardial infarction, as well as cause atrial interstitial changes that may lead to atrial fibrillation, thrombosis, and thromboembolism.

Transthyretin amyloidosis is caused by the deposition of oligomers and monomers from damage to the transthyretin tetramer. Isolated atrial amyloidosis is caused by amyloid produced from atrial natriuretic peptide. Early diagnosis and proper management are crucial to minimizing damage. Treatment options include chemotherapy, stem cell transplantation, and supportive care.[7]

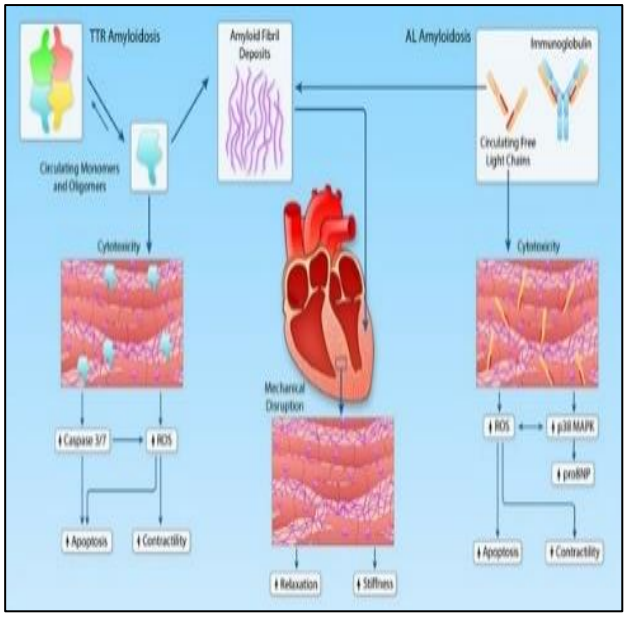

Figure 3: Mechanism of cardiac disfunction.[8]

Amyloid fibril deposition damages tissues, causes cellular injury, and ultimately leads to organ dysfunction. Amyloid deposits in CA are diffuse in AL amyloidosis and nodular in TTR amyloidosis, but both types cause thickening and stiffness of the biventricular wall, resulting in a restrictive myopathy and low cardiac output.[8]

Amyloidosis is a disease that affects various organs, including the heart, liver, kidney, and nervous system as we know and their being classified into various types helps us for better approach towards diagnosis and establishing the best possible treatment. There are six main types of CA, each with different symptoms and treatments. The disease usually develops after the age of forty and is more common in women. Symptoms may include dyspnea, palpitations, chest pain, and syncope, while physical examination findings may include periorbital purpura, macroglossia, fine lung crackles, and hepatomegaly. Accurate diagnosis requires immunohistochemistry and genetic testing, and treatment approaches and prognoses vary for each subtype. Amyloidosis is the most common cause of restrictive cardiomyopathy and can lead to angina, arrhythmia, syncope, and heart failure. Healthcare professionals should be aware of these potential symptoms and findings to ensure proper diagnosis and treatment of CA.[1,7,8-11]

CA is often accompanied by extracardiac manifestations, or "red flags," that can help identify the condition when combined with cardiac imaging findings. These include proteinuria, macroglossia, skin bruising, and carpal tunnel syndrome, among others. Additionally, heart failure, elevated NT-proBNP, unexplained right heart failure, pericardial effusion, persistent troponin elevation, low QRS voltage, and early conduction system disease are other potential indications of CA.[12]

Table 1: Red flags.[13]

Both subtypes of CA	AL-subtype	ATTR-subtype
Low voltage on ECG and thickening of septum/posterior wall>12 mm	HFpEF in combination with nephrotic syndrome	White male age ≥ 65 with HFpEF in combination with history of CTS and/or spinal stenosis
Thickening of RV free walls/valves	Macroglosia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of HTN
Intolerance of beta blockers or ACE inhibitors	Orthostatic hypotension	New diagnosis of HCM in an elderly patient
Low normal BP in patients with previous history of HTN	Peripheral neuropathy	New diagnosis of low flow/low gradient aortic stenosis in an elderly patient
History of bilateral CTS often requiring surgery	MGUS	Family history of ATTRm amyloidosis

Abbreviations: ECG: Electrocardiography; RV: Right ventricle; ACE: Angiotensin converting enzyme; HTN: Hypertension; CTS: Carpal tunnel syndrome; HFpEF: Heart failure with preserved ejection fraction; MGUS: Monoclonal gammopathy of undetermined significance; HCM: Hypertrophic cardiomyopathy.

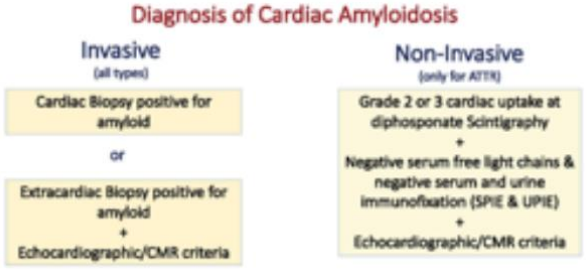

Figure 4: Invasive and non invasive methods of diagnosis.[12]

Cardiac amyloidosis is a condition that can be diagnosed through multiple non-invasive imaging techniques such as electrocardiography, echocardiography, cardiac magnetic resonance imaging, and nuclear scintigraphy. Each diagnostic method can provide unique insights that help to identify the condition and differentiate between different types of amyloidosis. In cases where specific diagnostic criteria are not met, extra-myocardial biopsy is required for accurate diagnosis and subtyping. Biopsy sites depend on the type of amyloidosis, with localized amyloidosis requiring samples from affected organs and systemic amyloidosis allowing biopsies from surrogate

sites. Mass spectrometry plays a crucial role in identifying amyloid deposits and subtypes. Although endomyocardial biopsy remains the gold standard for diagnosing cardiac amyloidosis, it has limitations such as low sensitivity and risk of major complications. Therefore, the value of endomyocardial biopsy depends on patient characteristics, and its accuracy can be influenced by patient selection and the number of tissue samples collected.[13,14]

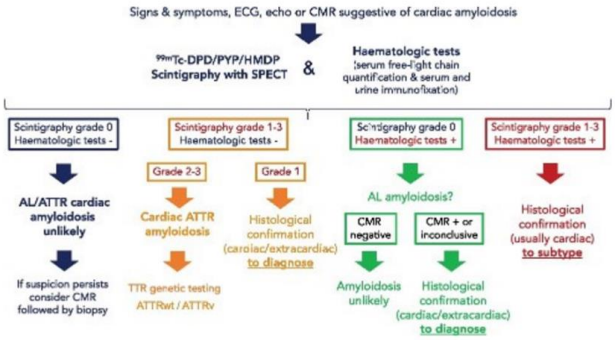

Figure 5: Diagnostic algorithm.[12]

Cardiac amyloidosis is a complex disease with several treatment options available, including therapies that target precursor protein production, stabilization, and degradation of amyloid fibrils. Some of the available treatment strategies for cardiac amyloidosis include blocking TTR synthesis, stabilizing TTR tetramers, and promoting clearance of TTR aggregates. Other strategies include knocking down precursor protein production, degradation/disruption of amyloid fibrils, and anti-seeding therapies. Hemodynamic profiling is essential to predict adverse outcomes, with reduced cardiac index (CI) and stroke volume index (SVi), and increased cardiac filling pressure. Overzealous diuresis should be avoided, considering the preload sensitivity in CA. Accurate diagnosis and tailored treatment strategies are essential for optimizing outcomes in patients with CA.[8,12-15]

Differences exist between AL and ATTR subtypes in terms of predictors of mortality. Atrial fibrillation is a significant prognostic factor in AL amyloidosis, while NYHA class III-IV symptoms and LV ejection fraction are associated with mortality in ATTR. Troponin T and NT-proBNP levels predict mortality in both subtypes. Markers of functional capacity and LV systolic function are more associated with death in ATTR than AL. However, no variable shows a significantly greater prognostic ability in one subtype over the other.[19]

CASE REPORT

The case under review pertains to a 61-year-old retired woman with a history of hypertension who reported heart palpitations, shortness of breath, and fluctuating blood pressure in December 2019. The patient had been regularly consuming lisinopril 10 mg once daily for hypertension management. Due to episode of palpitations, she was admitted to central district hospital by ambulance where she was diagnosed with paroxysmal atrial fibrillation.

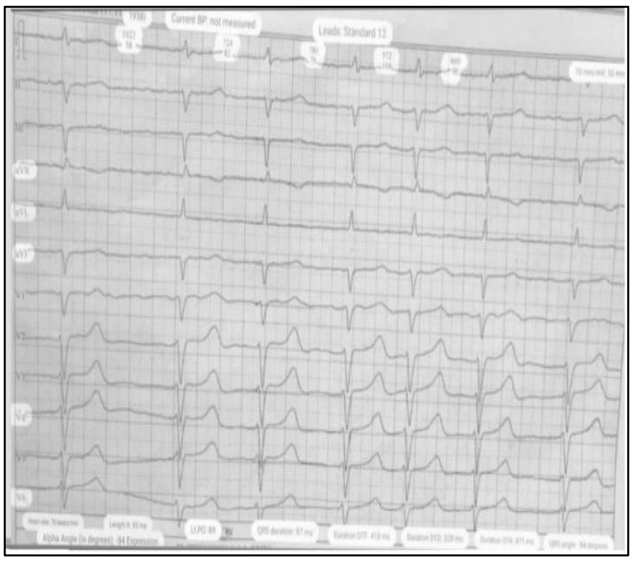

Figure 6: ECG in December, 2019.

The patient underwent electrical cardioversion to restore the sinus rhythm. However, due to recurring symptoms, radiofrequency ablation of the cavo-tricuspid isthmus was performed. During the hospitalization, various clinical and lab tests were conducted, which revealed coronary artery disease, atherosclerotic cardiosclerosis, and mitral valve insufficiency, Moderate fibrosis of the mitral valve leaflets and mitral regurgitation grade 2 were also noted.

Post-hospitalization, the patient was prescribed rivaroxaban 20 mg once daily for 3 months for anticoagulation transitioning to as Picard 75 mg once daily, amiodarone 200 mg once daily for antiarrhythmic control, metoprolol 50 mg for heart rate control, and rosuvastatin 10mg for reducing LDL values. She was advised to follow up closely with her healthcare providers for further management and monitoring.

In April 2022, the patient's condition deteriorated. Her condition was characterized by shortness of breath, palpitations, and heart failure. An electrocardiogram (ECG) taken on the same day revealed a paroxysm of atrial fibrillation (AF). She self-administered medication including propafenone and pan-angina to manage the symptoms. However, sinus rhythm was not restored. Therefore, she was transferred to the Grodno state clinical cardiological centre for further investigation. Trans-esophageal echocardiography revealed no mass formations in the heart cavities, so synchronized cardioversion with a biphasic defibrillator was performed, resulting in the restoration of sinus rhythm. Further investigations revealed concentric myocardial hypertrophy, and typical fibrosis patterns of the myocardium. The patient was prescribed metoprolol 25

mg, spironolactone 25 mg, losartan 100 mg, rosuvastatin 10 mg, rivaroxaban 20 mg, amiodarone 200 mg, and amlodipine 5 mg for various purposes.

The patient was advised on cardiac MRI, proteinogram, and consultation with a cardiologist at republican scientific and practical centre «cardiology». In May 2022 a cardiac MRI was performed, which revealed signs of cardiac amyloidosis, concentric myocardial hypertrophy, papillary muscle hypertrophy, pancreatic myocardial hypertrophy, typical fibrosis pattern of all heart chambers, and changes in the tissue characteristics of the left ventricular myocardium.

In October 2022, the patient was diagnosed with restrictive cardiomyopathy, cardiac amyloidosis, paroxysmal form of atrial fibrillation, moderate sinus bradycardia, hypertension 2, risk 4, H2A (NYHA FC II), and hypokalemia. hospitalization at the republican scientific and practical center "cardiology" was recommended for additional examination and verification of the diagnosis. The patient's treatment was also corrected, with nebivolol 2.5 mg, telmisartan 40 mg, eplerenone 50 mg, amiodarone 200 mg, and rivaroxaban 15 mg being prescribed until the GFR achieved this value: 45 ml/min/1.

In November, this patient was admitted to the republican scientific and practical center "cardiology" for medical consultation. Upon objective examination, the patient exhibited soft tissue swelling in the legs, muffled heart sounds, a heart rate of 56 beats per minute, and a blood pressure of 140/90 mm Hg, while other parameters were within normal ranges. Subsequently, laboratory tests were performed, which yielded various results, including those from the echocardiography and coronary angiography tests, to aid in establishing a definitive diagnosis.

The coronary angiography demonstrated no stenosis in the coronary arteries, a CAD-RADS score of 0, and a low cardiovascular score according to the Agatson scale. Additionally, a biopsy of the buccal mucosa was performed, revealing the presence of amyloidosis. The type of amyloidosis was determined to be AL-amyloidosis based on the weak focal expression of kappa light chains and no expression of lambda light chains in the immunohistochemistry test.

After verifying the diagnosis of AL-amyloidosis, department of hematology and transfusiology of state educational institution recommended a VCD regimen with a bortezomib dose reduction of 1 mg/m^2 for up to 6 cycles. First cycle of therapy was completed between January 30 and February 10, 2023, according to the VCD regimen, and was supplemented with various medications which included 40 mg furosemide, 8mg ondansetron, 200 mg acyclovir once a day, co-trimoxozole once a day. However, laboratory tests conducted after first cycle revealed elevated levels of BNP and creatinine, indicating chemotherapy-induced kidney damage.

The next scheduled treatment cycle was planned for March 2023, but the patient's health deteriorated before the scheduled treatment, and she was diagnosed with atrial fibrillation, which was treated with Novocain amide.

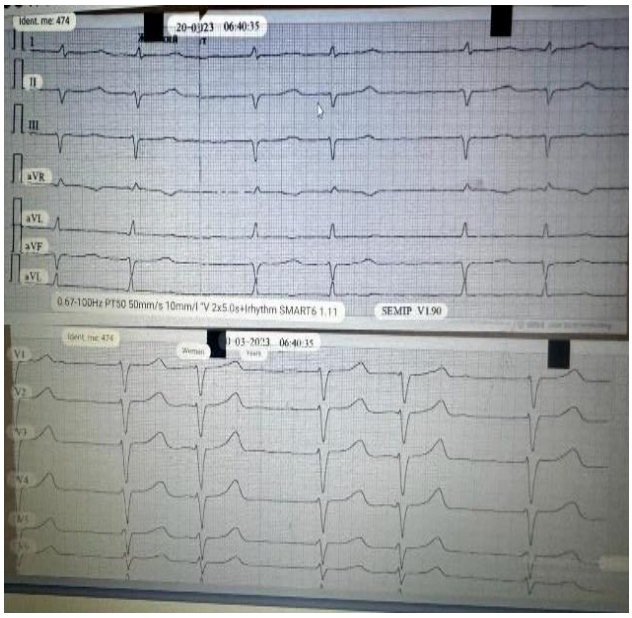

Figure 7: ECG at March, 2023.

However, the condition recurred within a few days and was treated similarly. Additional tests, including biochemical blood test, multi-organ USG and ECG, were conducted, revealing several abnormalities comprised of the following: liver and pancreas with elevated echogenicity, thyroid gland presented with reduced echogenicity and heterogenous echo-structure along with nodal formations, ventricular and supraventricular extrasystoles indicating arrhythmia, grade 1 transient atrioventricular block, PQ interval of up to 250 ms suggesting conduction abnormality.

Table 2: Lab tests, March 2023.

Parameters	Value	Normal range
Urea	5.78 mmol/l	2.2-8.3 mmol/l
Creatinine	79 µmol/l	53-97 µmol/l
Cholesterol	6.28 mmol/l	0-5.16 mmol/l
HDL	1.6 mmol/l	≥1.55 mmol/l
LDL	3.6 mmol/l	0-3.37mmol/l
Triglycerides	1.46 mmol/l	0-1.53 mmol/l
C-reactive protein	4.7 mg/l	0-6 mg/l
Total bilirubin	13.3 µmol/l	5-21 µmol/l
Blood glucose	5.6 mmol/l	3.3-5.9 mmol/l
Aspartate aminotransferase	20.2 U/l	0-31 U/l
Alanine aminotransferase	35.8 U/l	0-32 U/l
Sodium	135 mmol/l	135-145 mmol/l

To address these issues, the healthcare team recommended a series of measures, including follow-up by a cardiologist, therapist, or hematologist, a specific diet, compliance with the work and rest regimen, and dosed physical activity, among others. Furthermore, a regimen comprising several medications, including rivaroxaban based on CHADS2-VASc scale=4 points and HAS-BLED=1 point, eplerenone, nebivolol, amiodarone, empagliflozin, and omega-3, was prescribed to manage the patient's condition. Finally, the patient was advised to continue the course of polychemotherapy for AL-amyloidosis under the supervision of the healthcare institution at the Grodno university clinic, with monitoring of echocardiography and other metrics in place.

From this time, she was not hospitalized in Grodno cardiocenter and continued her treatment under the supervision of her local general practitioner.

DISCUSSION

The presented case report provides a comprehensive overview of the diagnostic journey and management challenges encountered in a patient with cardiac amyloidosis. Cardiac amyloidosis is a complex condition characterized by the accumulation of misfolded proteins in the heart tissue, leading to a range of clinical manifestations and diagnostic dilemmas.

The patient, who initially presented with symptoms suggestive of cardiac rhythm disturbances, including heart palpitations and shortness of breath, underwent a series of tests, including electrocardiograms and echocardiography.[20] These tests revealed characteristic findings indicative of cardiac amyloidosis, such as low voltage on electrocardiography and myocardial ventricular thickening seen in echocardiography, which are consistent with classical findings associated with amyloid infiltration of the myocardium.[21]

Of particular significance in this case was the histopathological examination, specifically myocardial biopsy, which played a crucial role in establishing a definitive diagnosis of cardiac amyloidosis.[22] This underscores the importance of tissue characterization in differentiating between different types of amyloidosis, such as AL and other types, which has significant implications for subsequent management strategies.

The challenges encountered in managing cardiac amyloidosis, such as the risk of chemotherapy-induced organ damage and recurrent arrhythmias, are well illustrated in this case.[23] The complexity of this condition necessitates personalized treatment plans tailored to the patient's unique clinical profile, as evidenced by the multidisciplinary approach taken in this case.

Furthermore, the discussion highlights the importance of recognizing and interpreting red flags associated with cardiac amyloidosis, such as peripheral neuropathy, macroglossia, and unexplained heart failure symptoms. When combined with imaging and laboratory findings, these red flags can aid in early detection and diagnosis of cardiac amyloidosis.

Overall, this case report serves as a valuable contribution to understanding cardiac amyloidosis and underscores the importance of a systematic approach to diagnosis and management. By drawing connections to classical findings observed in other patients with cardiac amyloidosis, this discussion enhances our appreciation of the complexities inherent in this condition and provides insights that can inform clinical practice and research efforts aimed at optimizing patient outcomes.

CONCLUSION

The case report emphasizes the essence of meticulous diligence and perseverance in patient care. It highlights the importance of a comprehensive diagnostic evaluation, personalized treatment strategies, and a multidisciplinary approach for optimal patient outcomes. The report also provides insights into the challenges associated with cardiac amyloidosis, including chemotherapy-induced organ damage and recurrent arrhythmias, and the need for further research efforts to refine therapeutic approaches for this complex disorder. Overall, the case report serves as a poignant reminder of the formidable power of persistence, collaboration, and tailored patient care in promoting better outcomes for patients with cardiac amyloidosis.

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