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Case report

Diagnostic problems of rare diseases — case report of amyloidosis

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ABSTRACT

Amyloidosis is a group of disorders characterised by the accumulation of insoluble proteins in tissues. These deposits lead to organ dysfunction and, in many cases, death. This paper discusses the case of a 61-year-old male patient who presented with fatigue, dyspnoea with minimal exertion and noncharacteristic abdominal cramping pain that had been present for three months. Laboratory tests showed abnormalities indicating cholestasis, liver and kidney damage, and hypercalcemia. Echocardiography revealed thickening of the left ventricular walls with preserved ejection function, a strongly hyperechoic interventricular septum. Despite intensive pharmacotherapy, the patient developed multiorgan failure and died due to the signs of hepatic encephalopathy and acute kidney injury. According to the autopsy report storage disease is suspected, and additional examinations revealed intercellular amyloid deposits (Congo Red +, Sinus Red +) in the heart muscle, spleen, and liver.

KEYWORDS

amyloidosis, multiorgan involvement, cardiac amyloidosis, diagnostic challenges of amyloidosis

INTRODUCTION

Amyloidosis is a group of disorders characterised by the accumulation of insoluble proteins in tissues. The most common form of systemic amyloidosis is light chain amyloidosis, which is composed of the light chains of immunoglobulins. These deposits lead to organ dysfunction and, in many cases, death [1]. The most clinically relevant systemic types in adults are light-chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. AL remains the predominant and most severe form because of its rapid progression and multisystem involvement [2].

The symptoms are not specific and depend on the organs affected. Since essentially any organ system can be affected, the disease is progressive and the presentation is variable, with delays in diagnosis being common [3]. Early nonspecific features commonly include constitutional symptoms such as fatigue and unintended weight loss. Organ-specific manifestations include nephrotic-range proteinuria and oedema resulting from renal involvement; restrictive cardiomyopathy, heart failure and arrhythmias resulting from cardiac involvement; peripheral and autonomic neuropathies (including orthostatic hypotension); and a variety of gastrointestinal signs, such as malabsorption and motility disorders, resulting from GI tract involvement. The most common findings when the liver is involved are hepatomegaly and a cholestatic pattern in liver biochemistry (particularly elevated alkaline phosphatase, often out of proportion to transaminases). Classic single-centre series and clinicopathologic studies have reported hepatomegaly in the majority of patients with documented hepatic AL amyloid (for example, hepatomegaly has been reported in >80% of patients with hepatic AL involvement in older series), and persistent ALP elevation is a common laboratory

hallmark. Clinical manifestations can be deceptive and are often recognized at an irreversible stage. For this reason, amyloidosis is still underdiagnosed [4]. Cardiac amyloidosis is the main factor affecting survival, and the earlier it is detected, the better the prognosis [5,6].

Rare as the disease is, more cases are being diagnosed as a result of improved detection method, greater clinician awareness and better diagnostic methods. Contemporary epidemiological analyses suggest that the incidence and prevalence of AL amyloidosis have increased over the last decade, likely due to greater recognition, wider use of diagnostic testing and genuine increases in detection. Recent large registry and EHR analyses estimated the incidence of AL in adults to be around 16.7 cases per million person-years in the US in 2021, with an increasing diagnosed prevalence in recent years [7]. Epidemiological data on amyloidosis show geographical variation. Older literature and reviews from Europe and North America frequently cite a rate of 5–12 cases per million per year for all systemic types combined, and 10 cases per million per year for AL specifically. We have limited but informative Poland-specific data. A national analysis of non-hereditary amyloidosis in Poland reported an incidence of approximately 2.49 cases per million person-years. There was a slightly higher risk in men, and the majority of cases were coded as of an undetermined (non-hereditary) aetiology. The authors noted likely under-ascertainment due to delayed diagnosis and insufficient awareness [8,9].

CASE REPORT

A 61-year-old man was admitted to the hospital with significant weakness, reduced exercise tolerance and atypical abdominal cramping pain of 3 months' duration. In addition, the patient had reported yellow discoloration of the skin and eyes for approximately 2 weeks. Toxic liver injury was suspected on admission. Family history revealed that his father died of "cancer of unknown origin".

The laboratory tests revealed many abnormalities, what was summarized in the table 1. Alanine transaminase (ALT): 64 U/L (normal range: <50), Aspartate trans-aminase (AST): 106 U/L (normal range: <50), Gamma-glutamyl transferase (GGT): 705 U/L (normal range: <60), Alkaline phosphatase (ALP): 993 U/L (normal range: 40–129). Total bilirubin: 77 mg/dL (normal range: 0.3–1.2), total protein 4.52 g/dL (normal range: 6.6–8.3), albumin 2.93 g/dL (normal range: 3.5–5.2), and total cholesterol 320 mg/dL (normal range: <190). Other laboratory tests revealed an increased concentration of D-dimer (14,477 ng/ml, normal range <500), B-type natriuretic peptide (pro-BNP) (2,886 pg/ml), an increased stable troponin concentration (180 ng/L, normal range <14.5) and creatine kinase MB isoenzyme (CK-MB) (40 U/L, normal range <25). In serum – lambda chains (+) were found. In urine examination proteinuria (150 mg/dL) and bilirubin (6 mg/dL) were detected.

Parameter	Value	Normal range
Alanine transaminase (ALT)	64	<50 U/L

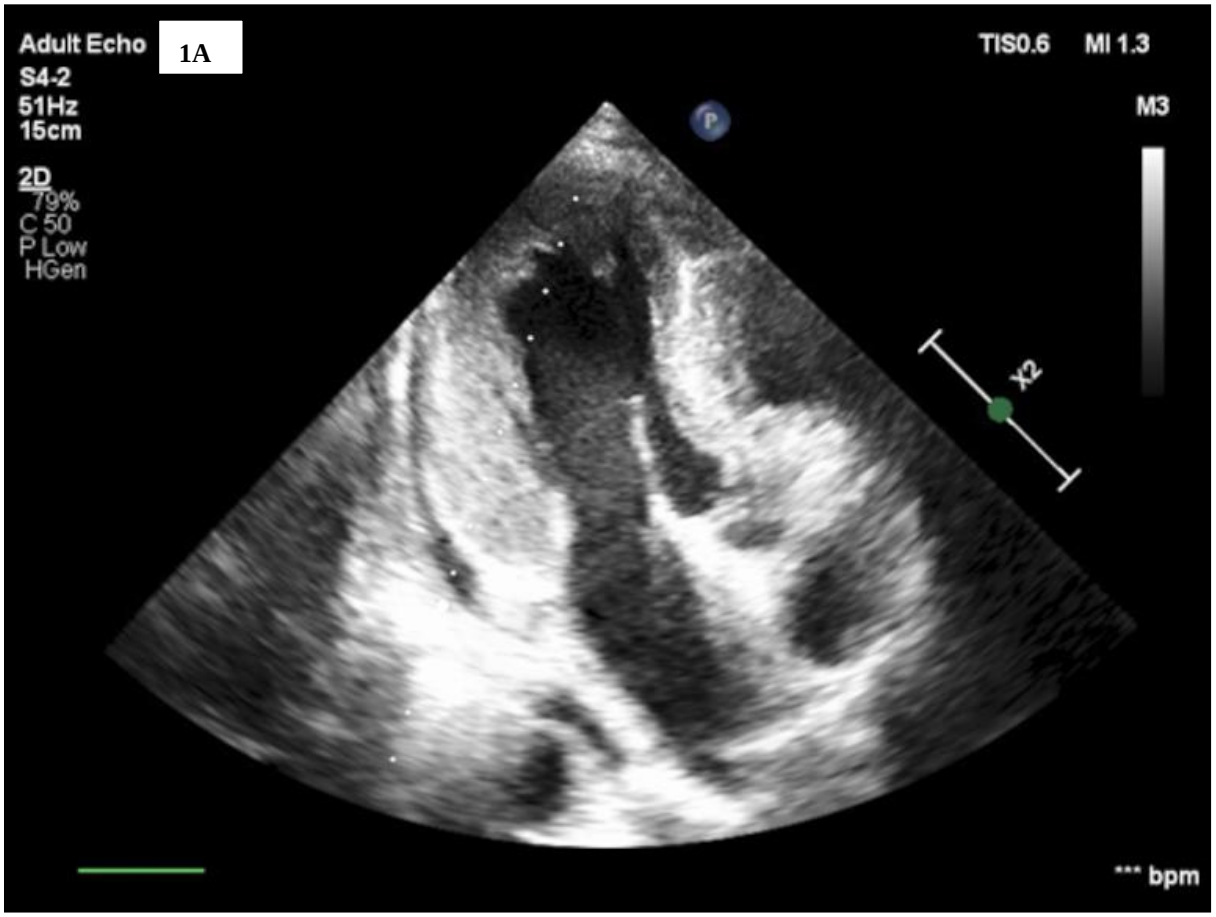
Aspartate transaminase (AST)	106	<50 U/L
Gamma-glutamyl transferase (GGT)	705	<60 U/L
Alkaline phosphatase (ALP)	993	40-129 U/L
Creatinine	1.09	0.67-1.17 mg/dL
GFR	75,5	>60 ml/min
Total bilirubin	7.7	0.3-1.2 mg/dL
Direct bilirubin	9.02	0-0.2 mg/dL
Total protein	4,52	6.6-8.3 g/dL
Albumin	2.93	3.5-5.2 g/dL
Total cholesterol	320	<190 mg/dL
D-dimer	14,48	< 500 ng/mL
B-type natriuretic peptide (pro-BNP)	2886	<125 pg/mL
Troponin concentration	180	<14.5 ng/L
Creatine kinase MB isoenzyme (CK-MB)	40	< 25 U/L
PSA:	1.03	5.71–26.3 ng/ml
CA 19.9	39	<27 U/ml
CEA	5,86	<5.0 ng/ml
Vitamin B12	3262	197-771 pg/ml
Total calcium level	13,2	8.8-10.2 mg/dl
Ionised calcium level	1.87	1-1.4 mmol/l
Calcium concentration in the daily urine collection	770	100-300 mg/DZM
Parathyroid hormone (PTH)	9.24	15-65 pg/ml

The ECG result was normal.

A computed tomography (CT) scan of the chest using a protocol for pulmonary embolism (PE) was negative, but showed small-to-moderate bilateral pleural effusions, atelectatic lesions bilaterally in the lower lobes and supradiaphragmatically, and fibrous lesions bilaterally in the lung apexes.

A CT scan of the abdomen and pelvis with contrast revealed a liver with signs of impaired perfusion. There was fluid around the liver, near the spleen, and in the pelvis. The gallbladder was normal size with a thickened wall, probably due to adenomyomatosis, and there were numerous small calcified deposits in the cervical area. The pancreas was normal size, but a hypodense area of approximately 7 mm was visible in the tail, suggesting branch-duct intraductal papillary mucinous neoplasms (BD-IMPN). The prostate gland was enlarged and heterogeneous. There was long-term thickening of the small intestinal wall to approximately 5 mm in the distal area, suggesting inflammatory/reactive changes. The examined skeleton showed signs of osteopenia. Additionally, calcified atherosclerotic plaques were found in the abdominal aorta and iliac arteries.

A transthoracic echocardiogram showed concentric hypertrophy of the left ventricle - interventricular septal enlargement at 18 mm (6-9 mm), posterior wall at 20 mm (6-9 mm), severely hyperechoic interventricular septum, mild mitral regurgitation and a small amount of fluid in the pericardial sac. Tissue Doppler imaging (TDI) of the basal interventricular septum showed reduced early diastolic velocity (e'). Left ventricular ejection function was preserved (LVEF 52%) (Figure 1A-E).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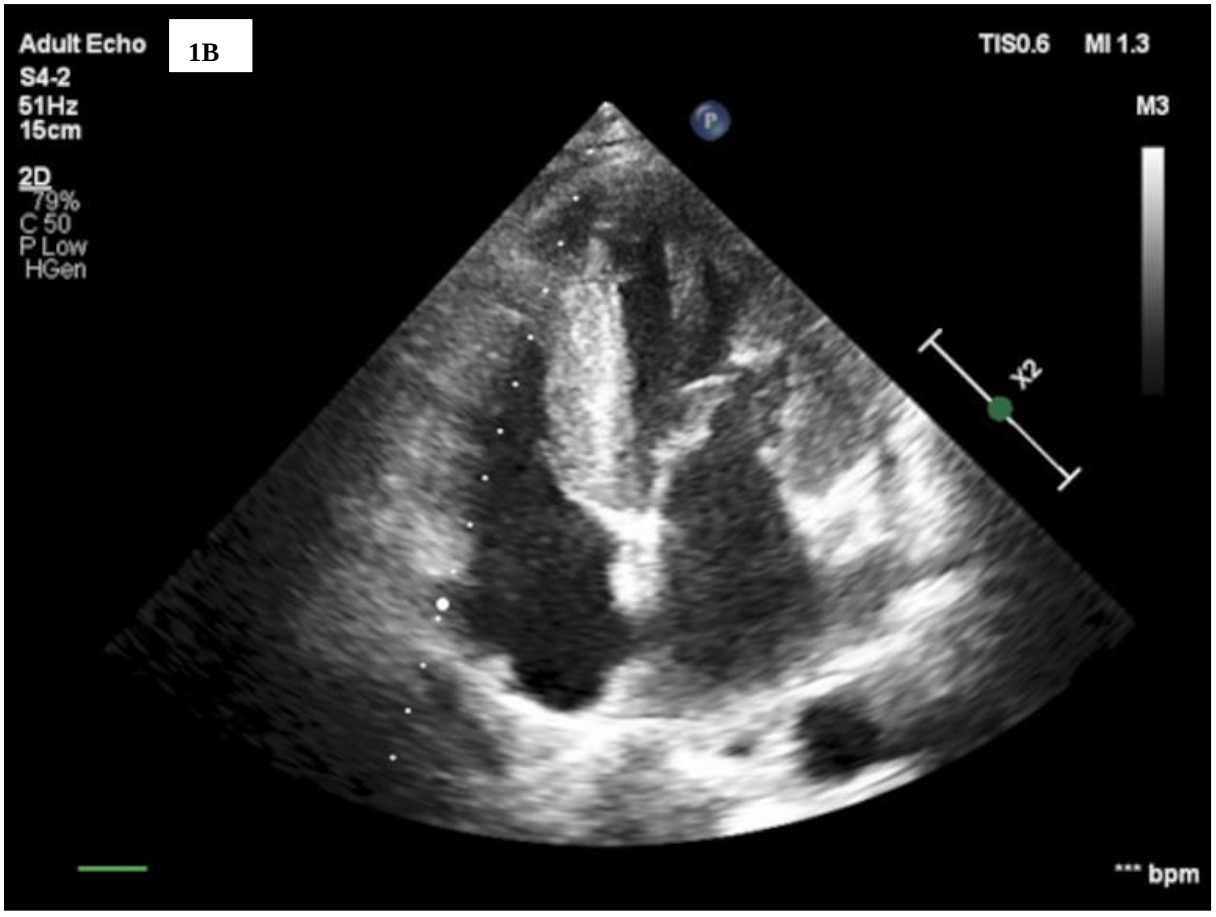
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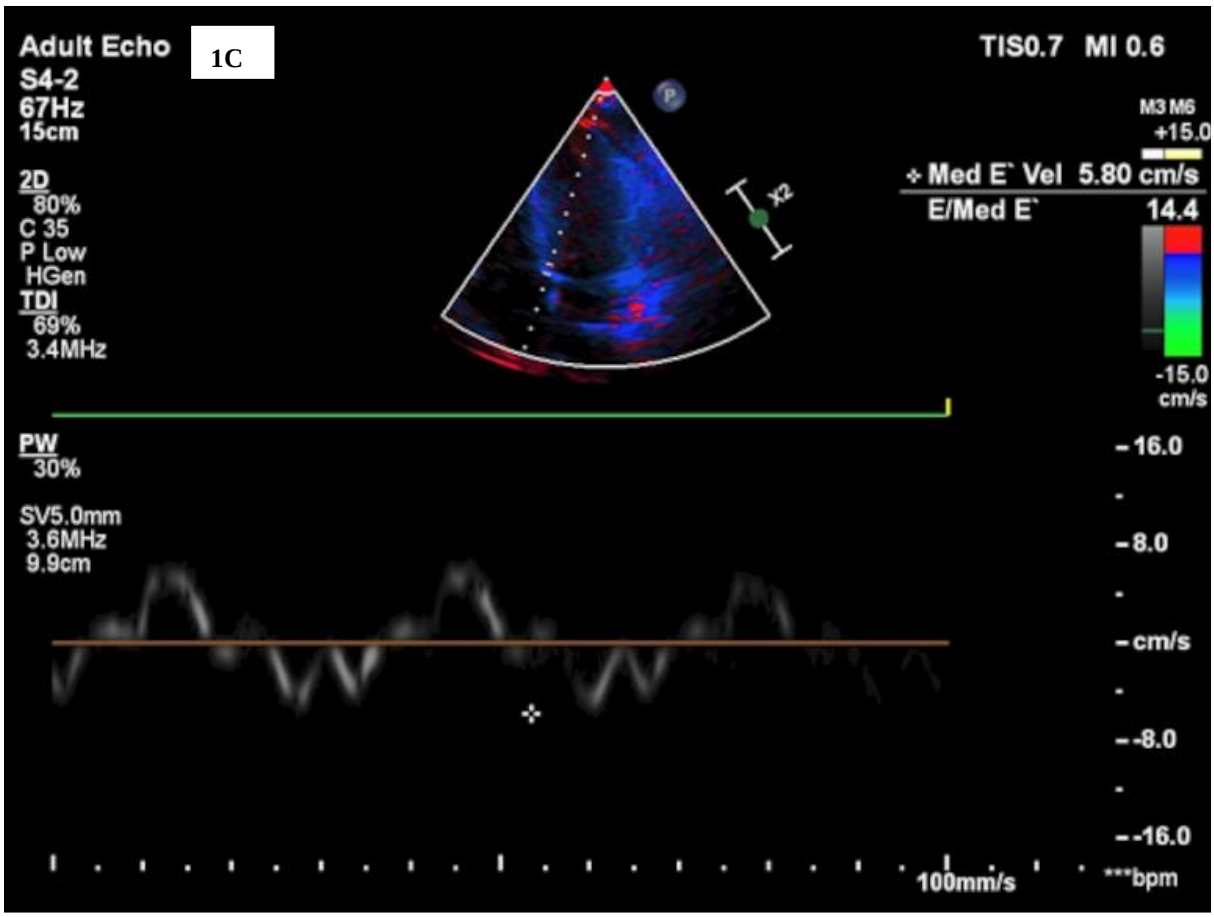
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3.6MHz
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TIS0.7 MI 0.6
M3 M6
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Med E` Vel 5.80 cm/s
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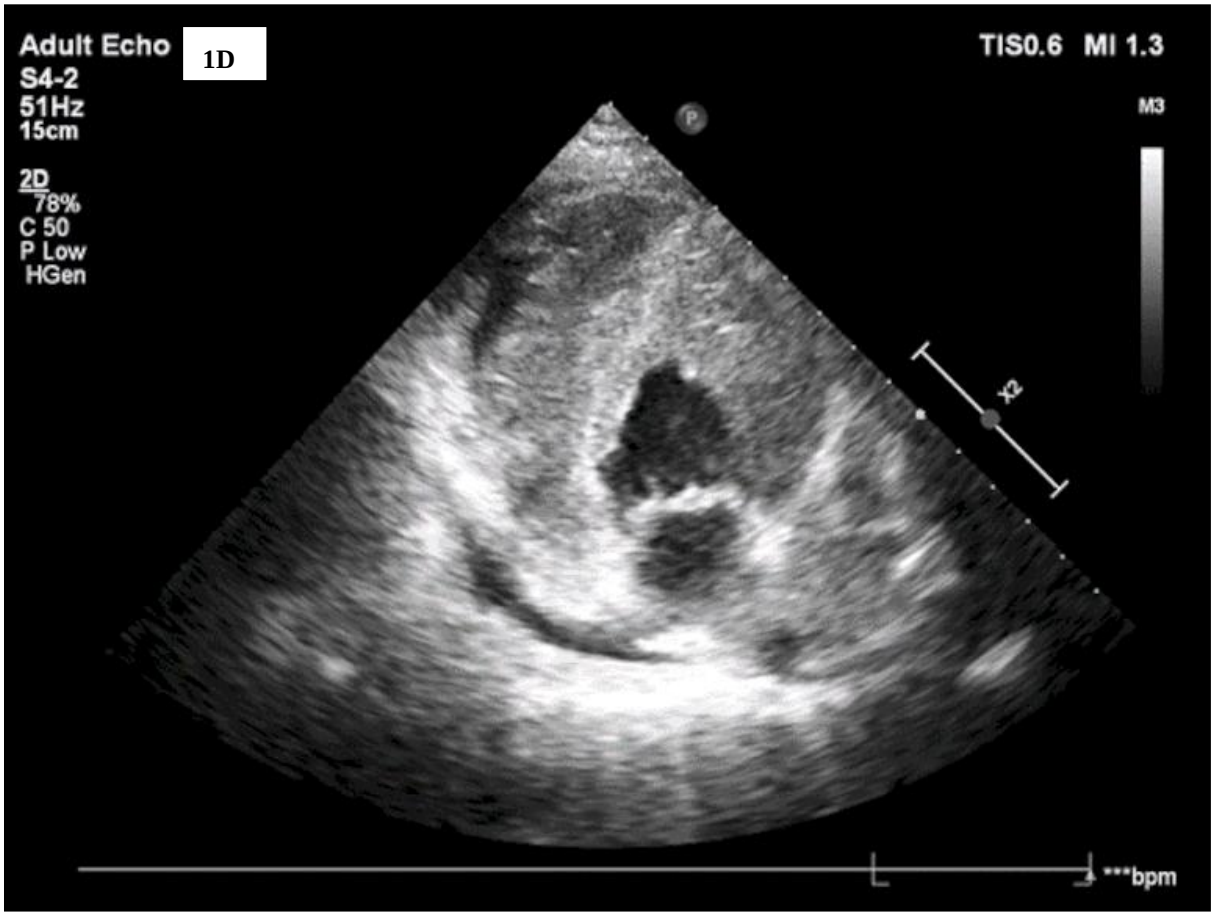

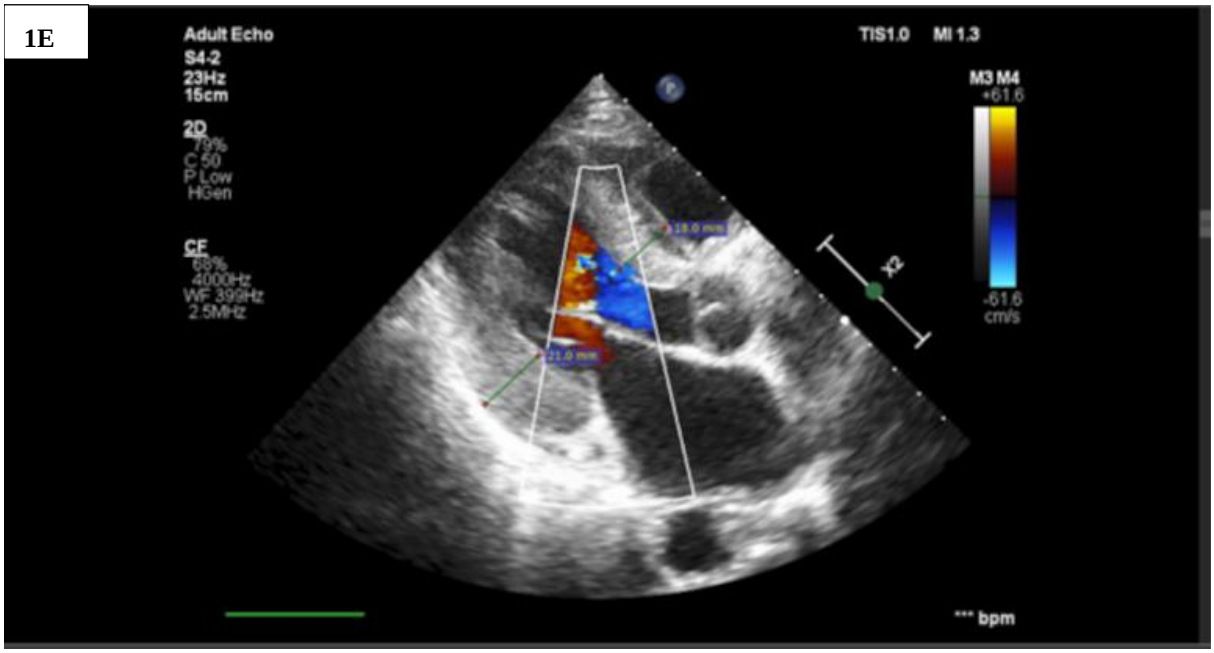

Fig. 1. (A) Apical 3 chamber view. Hypertrophy of the left ventricular walls and fluid in pericardium. (B) Apical 4 chamber view in end-diastole. (C) Tissue Doppler imaging- mitral annular diastolic velocity, (D) Parasternal short axis view, (E) Reduced early diastolic mitral annular velocity.

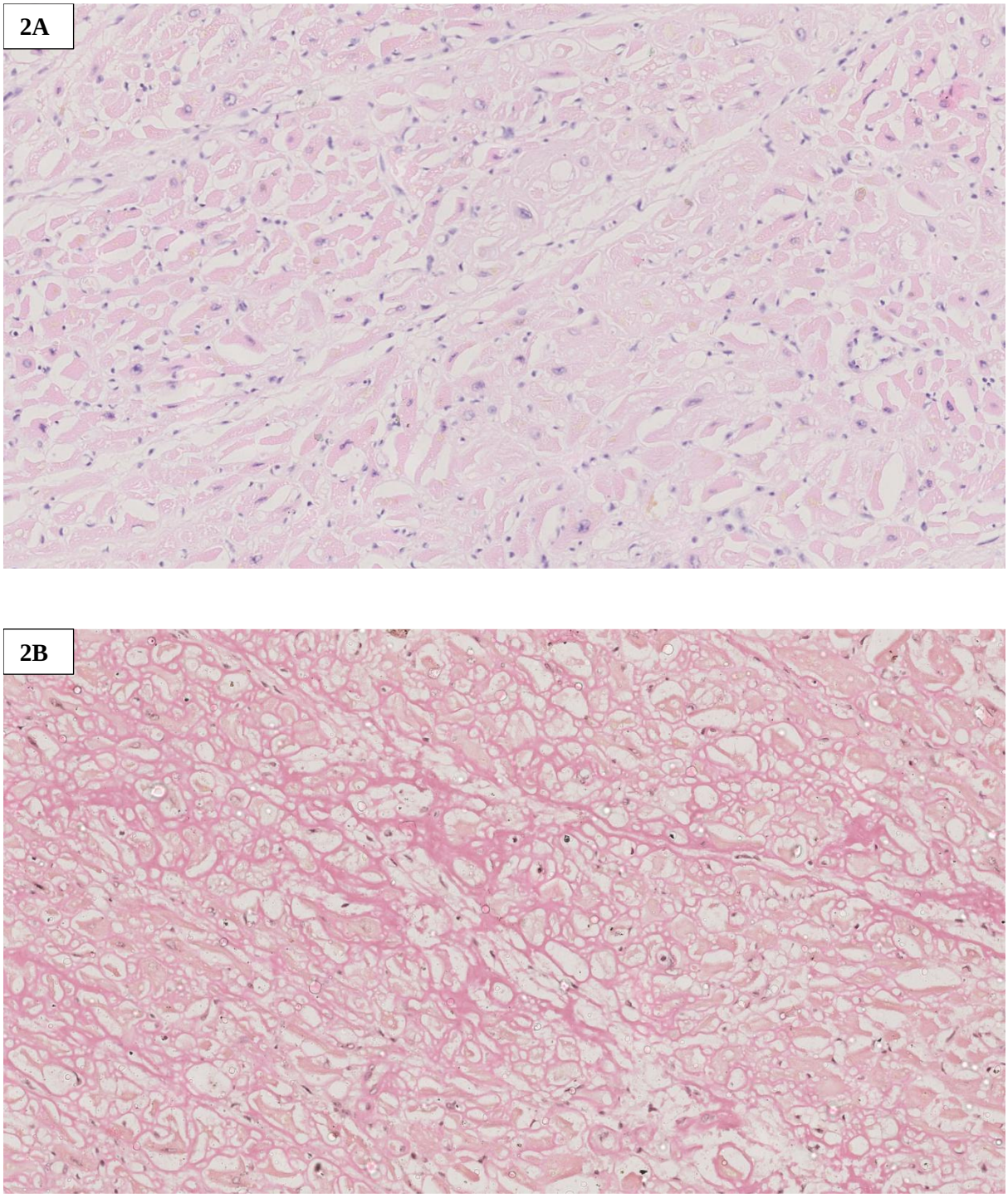

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Fig. 2. (A) Hematoxylin and eosin staining in heart tissue. (B) Sirius Red staining in heart tissue.

The differential diagnosis ruled out HIV, syphilis, tuberculosis, hepatitis B and C and systemic connective tissue diseases (ANA, pANCA and cANCA profiles were negative). Tumor markers were determined: PSA, Ca 19-9, CEA. Additional laboratory tests revealed an increased vitamin B12 concentration, hypercalcemia with elevated calcium concentration in the daily urine collection, alongside a reduced parathyroid hormone (PTH) concentration (Table I).

Initially, hypercalcaemia was treated with parenteral hydration, bisphosphonate and steroid therapy, resulting in normalisation of serum calcium levels. Due to PTH-independent hypercalcaemia,

suspicion of osteolytic lesions, and the patient's medical history, extensive cancer diagnostics were initiated. No pathological changes were visible in the skull X-ray.

In serum – lambda chains (+) were found but immunofixation of proteins was performed and no free light chains were detected in the urine, nor was any plasma cell infiltration detected in the bone marrow biopsy.

Due to signs of liver damage and jaundice, magnetic resonance cholangiopancreatography (MRCP) was performed, revealing no dilated intrahepatic bile ducts or enlarged gallbladder. Adenomyomatosis was suspected near the bottom of the gallbladder.

Due to increasing cholestasis symptoms and the patient's deteriorating condition, a gastroscopy was conducted, revealing candidiasis-like lesions throughout the oesophagus, an irregular Z-line with three erosions up to 6–7 mm long (Los Angeles B classification), signs of gastritis and several small polyps in the stomach, which were removed, as well as two flat pyloric ulcers.

Following gastroscopy, the patient reported shortness of breath and increasing weakness, and appeared sleepy. The following were found: hypotension (80/46 mmHg), capillary blood saturation (93%), glycaemia (60 mg%) and body temperature (38°C). A physical examination revealed tenderness in the right lower rib area. Passive oxygen therapy was started using a reservoir mask and hydrocortisone and 5% glucose were administered. Blood and urine samples were collected for culture. An urgent CT angiogram of the pulmonary arteries was performed, which revealed no embolic material in the arteries; however, fluid was visualized in the pleural cavities, measuring up to 22 mm on the right and 27 mm on the left.

A CT scan of the abdomen and pelvis with contrast revealed a heterogeneous liver in a multiphase examination, primarily due to perfusion disorders. The hepatic veins were not contrasted in any phase of the examination, which was primarily due to organ hypoperfusion; thrombotic changes were less likely. The adrenal glands showed intensive post-contrast enhancement, as in the case of hyperperfusion due to shock.

Following an anesthetic consultation, he was transferred to the Intensive Care Unit (ICU). During his stay in the ICU, increasing coagulation abnormalities were observed, as well as a further increase in cholestatic parameters, a slight increase in C-reactive protein concentration (max. 47.8 mg/dL (normal range: <5.0)) and positive procalcitonin (14 ng/mL (normal range: <0.5)). There was also a tendency to spontaneous hypoglycemia. The overall clinical picture suggested acute liver failure and septic shock of unknown origin. Treatment included pressor amine infusion, wide-spectrum antibiotic therapy, steroid therapy, intensive fluid therapy and oxygen therapy. The patient underwent a gastroenterological consultation and a biliary tract infection was suspected.

Gastroscopy again revealed no signs of active bleeding and the visible biopsy sites were covered with clots. ERCP was performed during which sphincterotomy was carried out and the results suggested a purulent infection.

Staphylococcus aureus MSSA, Citrobacter freundii ESBL(-) and Klebsiella pneumoniae ESBL(-) were cultured in blood samples.

Due to signs of hepatic encephalopathy, treatment included lactulose and rifaximin and the patient underwent dialysis. Despite intensive pharmacotherapy, the patient developed multi-organ failure and died.

The autopsy report revealed cardiac hypertrophy and stiff myocardial walls with a blurred fiber structure. Additionally, the liver was enlarged and its parenchyma had a disturbed architecture, appearing stiff and granular. There was acute pancreatitis with foci of Balser's necrosis in the head and tail of the pancreas. Storage disease is suspected, and additional examinations revealed intercellular amyloid deposits (Congo Red +, Sinus Red +) in the heart muscle, spleen and liver (Figure 2).

DISCUSSION

The aim is to achieve early diagnosis of amyloidosis, for which education efforts should be made to raise awareness among doctors of various specialties. If diagnosed early, morbidity and mortality can sometimes be limited. In D'Souza's study, the median number of precursor diagnoses was five, with dyspnoea and fatigue being the most prevalent. The time from the first occurrence of a precursor to an AL diagnosis ranged from 3.2 to 21.4 months [10]. A diagnosis should be considered for patients with a multisystem disorder involving the heart, kidneys, liver or nervous system.

Initially, our patient reported non-specific symptoms such as weakness and easy tiredness. Secondly, he exhibited symptoms of liver damage and heart failure. Many of the doctors who consulted the patient believed that liver toxicity was the cause of all his symptoms. The signs of gastrointestinal (GI) amyloidosis often resemble those of other GI disorders. Hepatic involvement is common in AL amyloidosis [11,12]. When the liver is involved, the most frequent objective findings are hepatomegaly and a cholestatic pattern in liver biochemistry (particularly elevated alkaline phosphatase, often out of proportion to transaminases) [13]. Jaundice is rare, but indicates a poor prognosis. Prognosis in patients with hepatic involvement is largely governed by concurrent cardiac or renal disease rather than liver dysfunction alone [14].

The patient's enlarged liver was also due to heart failure. Echocardiography revealed an image of the myocardium that is typical of amyloidosis, which led to the suspicion of amyloidosis [15]. The prognosis for patients with myocardial involvement is very serious. Cardiac amyloidosis is often the best predictor of mortality and morbidity in systemic amyloidosis compared with involvement of other organs [16]. Once diagnosed, treatment options are limited. The presence of heart failure at the time of diagnosis, as in this case, is associated with a median survival of just 6 months for patients with AL amyloidosis who have not received hematologic treatment [15]. Cardiac hypertrophy can have various causes, ranging from genetic disorders such as hypertrophic

cardiomyopathy to changes resulting from mechanical factors such as severe aortic stenosis, arterial hypertension or temporary expansion of muscle tissue as seen in the 'athlete's heart'. In this case, although there was a history of hypertension, it was optimally treated. There were also no early cardiac deaths in the family, indicating that the cause of the cardiac condition could have been a metabolic storage disease, especially considering the overall clinical picture. However, morbidity and mortality in these patients are often due to disease elsewhere [18].

The immediate cause of death in this case was sepsis and multi-organ failure. ERCP examination after incision of the ampulla of Vater revealed purulent discharge, suggesting infection in the biliary tract, which likely caused sepsis. Gastrointestinal amyloidosis may indirectly increase the risk of biliary tract infections, as amyloid accumulation can disrupt normal intestinal peristalsis, impair bile flow, and lead to other complications, creating a more favorable environment for infection. The patient also could experience bile retention [18].

If the patient had undergone a liver or heart biopsy, this would have enabled the diagnosis of cardiac amyloidosis and facilitated the therapeutic decision. It is widely known, that localization in the heart often poses a diagnostic challenge [19]. Usually, it presents with jaundice, hepatomegaly, peripheral edema, and ascites, but it also can be asymptomatic [20]. Unfortunately, early signs are not given enough importance compared to cardiac ones [21].

Our work was limited by the lack of subcutaneous tissue or organ biopsy and the lack of amyloid typing. However, amyloidosis was suspected based on an echocardiogram performed during the final stage of the patient's stay in our department. Some results, including light chains, require several days to be obtained and a scintigraphy scan was impossible to perform in the patient's critical condition.

In summary, early detection of discrete signs of organ damage, but occurring simultaneously (impaired renal function, slight proteinuria, clinical symptoms suggesting heart failure or increased aminotransferase activity) should raise the suspicion of a chronic factor, including amyloidosis. Our real-life case will contribute to a better understanding and prompt suspicion, leading to an earlier diagnosis and management.

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