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CASE REPORT
Heart failure

Unicentric Castleman's disease associated with malignant cardiac Amyloid-A amyloidosis: a case report

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Background Unicentric Castleman's disease (UCD), a lymphoproliferative disorder characterized by enlargement of the lymph nodes, is a rare cause of Amyloid-A amyloidosis. While patients usually present with impaired kidney function and proteinuria, heart involvement is neither common nor the main cause of signs and symptoms.

Case summary We present a patient who was admitted to the hospital for impaired exercise capacity. Diagnostic work-up revealed severe left ventricular hypertrophy suggestive of cardiac amyloidosis. Although Congo red staining of endomyocardial biopsies was initially negative, subsequent immunohistochemical staining against serum amyloid A finally confirmed the diagnosis of cardiac amyloidosis. 18F-fluorodeoxyglucose positron emission tomography/computed tomography revealed a tumour located in dorsal of the duodenum. Fine-needle aspiration biopsy of the tumour was suggestive but could not confirm the presence of UCD beyond reasonable doubt. Rapid worsening of heart failure symptoms warranted urgent surgical tumourectomy, which resulted in immediate post-operative lowering of serum amyloid protein. However, post-operative cardiogenic shock could not be stabilized even with veno-arterial extracorporeal membrane oxygenation, and the patient eventually died. The UCD of the hyaline vascular (HV) subtype was confirmed by pathologic work-up of the excised tumour.

Discussion This case report presents for the first time a patient with malignant cardiac Amyloid-A amyloidosis caused by unicentric Castleman's disease of the HV subtype. Since the disease progresses swiftly, rapid diagnosis is essential for potential curative treatment.

Keywords Amyloidosis • Serum amyloid A • Heart failure • Unicentric Castleman's disease • Case report

ESC curriculum 2.1 Imaging modalities • 2.5 Nuclear techniques • 6.1 Symptoms and signs of heart failure • 6.5 Cardiomyopathy • 6.9 Cardiac dysfunction in oncology patients

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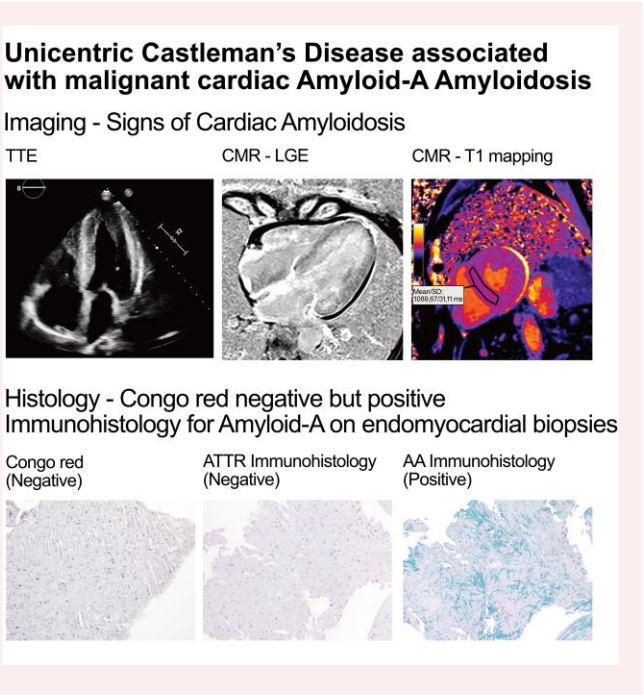
Learning points

- Unicentric Castleman's disease (UCD) of the hyaline vascular (HV) subtype is a rare cause of Amyloid-A amyloidosis.
- Up until now, cardiac involvement was not reported in UCD-HV patients with Amyloid-A amyloidosis whereas in this patient, the heart was the predominantly affected organ.
- Congo red staining of histological specimens with Amyloid-A amyloidosis can be ambiguous. Immunohistochemical staining against serum amyloid A is recommended in patients with clinically suspected amyloidosis, if more common types of amyloidosis were excluded.

Introduction

Castleman's disease (CD), a lymphoproliferative disorder, is a rare cause of Amyloid-A (AA) amyloidosis (AAA). Two forms of CD are described, unicentric (UCD) and multicentric CD. In UCD, either a single lymph node or multiple lymph nodes within a single lymph node station are affected.[1] Histologically, three subtypes of CD are distinguished, depending on the presence of interfollicular infiltration of plasma cells (PC subtype), their absence [hyaline vascular (HV) subtype], or a mixed subtype.[1] Patients with AAA usually present with impaired renal function and proteinuria. Cardiac involvement is neither common nor a cause of signs and symptoms at initial presentation.[2–4]

Summary figure



Case presentation

A 64-year-old male with Grade I arterial hypertension was referred to a community hospital for three months of exertional dyspnoea. Physical examination showed no congestion or other notable abnormalities. Family history was inconspicuous.

Lab studies revealed elevations of C-reactive protein [CRP, 12.9 mg/dL (<0.5 mg/dL)] and erythrocyte sedimentation rate [82 mm/h (0–20 mm/h)], normal leukocyte count, and microcytic anaemia (haemoglobin 11.4 g/dL [13–17.5 g/dL]; mean corpuscular volume 69.5 fL [80–99 fL]). The glomerular filtration rate was normal with no significant proteinuria and without evidence for monoclonal protein in serum or urine. A one-week treatment with ceftriaxone did not alter the inflammatory parameters. Extensive diagnostic work-up including gastroscopy, colonoscopy, computed tomography (CT) of the thorax and the abdomen, dental inspection, and blood cultures revealed no evidence of a source of infection. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was slightly elevated [340 ng/L (<210 ng/L)] whereas high-sensitive troponin-T was within normal limits. Electrocardiogram (ECG) showed signs of left ventricular hypertrophy (*Figure 1A*) that was confirmed by echocardiography. These results were corroborated by cardiac magnetic resonance imaging (CMRI; *Figure 1D*), and cardiac amyloidosis was considered as a potential diagnosis. ATTR amyloidosis was excluded by DPD scintigraphy. Furthermore, the free light chain ratio and immunofixation were normal, and bone marrow histology was unremarkable.

Congo red staining was repeatedly negative on endomyocardial biopsies (*Figure 1F*), but Masson's Trichrome staining was suspicious for amyloidosis in addition to interstitial fibrosis (*Figure 1E*, different purple/blue colours). Immunohistology for ATTR amyloidosis was negative (*Figure 1I*) but revealed marked deposits of amyloid protein A (AA) in the myocardial interstitium and in vessel walls (*Figure 1J*). Cardiomyocytes did not show hypertrophy or disarray. The number of $CD3^+$ T lymphocytes ($15/mm^2$) but not that of CD68+ macrophages was slightly increased.

Importantly, the presence of a systemic AAA was confirmed in histopathological biopsy specimens of the salivary gland, the subcutaneous fat pad, and the upper gastrointestinal tract as well as by proteome analysis by liquid chromatography with tandem mass spectrometry. Serum amyloid A (SAA) level was 561 mg/L [0–6.4 mg/L].

18F-fluorodeoxyglucose positron emission revealed marked tracer-uptake near the duodenum corresponding with a 4 cm retroperitoneal tumour. An endoscopic ultrasound-guided fine-needle biopsy showed amyloid deposits and lymphoid cells. Unicentric Castleman's disease was suspected, but the pathologic specimen did not allow for a definitive diagnosis.

The patient's heart failure symptoms worsened steadily during the prolonged aetiologic work-up from NYHA functional class II to NYHA functional class IV, accompanied by increasing NT-proBNP levels (>70 000 ng/L). Standing upright was associated with dizziness and repeated collapses. Therefore, the patient was transferred to our tertiary hospital.

Repeated imaging studies confirmed former results. Echocardiography showed a left ventricular ejection fraction of 63%, severely reduced global longitudinal strain (−4.1%) with apical sparing, 3rd degree diastolic dysfunction (E/lateral E′ 22.6), severe biventricular hypertrophy (interventricular septum thickness 23 mm) and minimal pericardial effusion (*Figure 1B* and *C*, Supplementary material online, *Videos S1* and S2). Diffuse late gadolinium enhancement was visualized on CMRI (*Figure 1E*). An extracellular volume (ECV) of 40% and a T1-relaxation time of 1090 ms were measured (*Figure 1F*). C-reactive protein and Interleukin-6 were elevated at 12.05 mg/dL and 67.7 ng/L [<7.0 ng/L], respectively. Procalcitonin was within normal limits. The patient tested negative for Human Immunodeficiency Virus, Hepatitis Virus A, B, and C. A test for Human Herpesvirus 8 (HHV8) was not performed.

Due to the critical clinical course, it was decided to perform urgent surgical tumourectomy with partial resection of the duodenum. The patient underwent abdominal surgery with cardiac surgeons on stand-by for

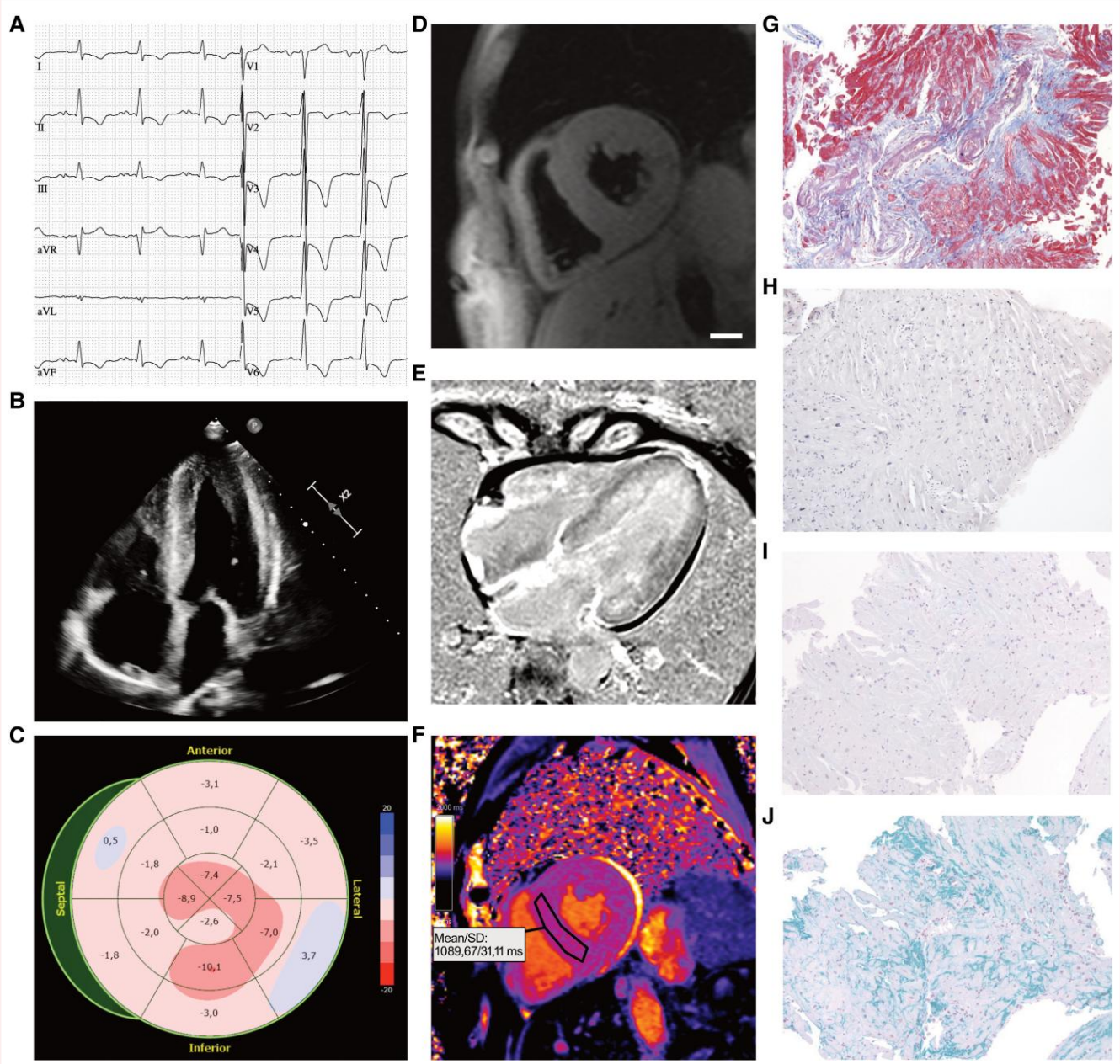


Figure 1 (*A*) ECG of the patient at presentation. The ECG is highly unusual for amyloidosis, where low voltages are common, whereas this ECG is suggestive of hypertrophic cardiomyopathy (HCM). (*B*) Echocardiographic apical four-chamber view exhibiting marked left- and right-ventricular hypertrophy. (*C*) Bull's eye plot of echocardiographic left ventricular global longitudinal strain (GLS) measurements. The GLS is severely reduced with −4.1%. Typical apical sparing can also be observed. (*D*) Cardiac MRI scan depicting extensive left ventricular wall thickening. Scale bar indicates 2 cm. (*E*) Cardiac MRI scan depicting diffuse late gadolinium enhancement. (*F*) T1 mapping of Cardiac MRI scan. T1-relaxation time was measured with 1090 ms in the interventricular septum. An ECV of 40% was measured. (*G* to *J*) Histological staining of myocardial biopsies; magnification 100×. (*G*) Masson's Trichrome staining. Red colour indicates cardiomyocytes, and blue indicates fibrosis/amyloidosis. (*H*) Congo red staining (negative). (*I*) Negative ATTR immunohistochemistry. (*J*) Positive Amyloid-A immunohistology; green/cyan represents amyloid deposits.

implantation of veno-arterial extracorporeal membrane oxygenation (vaECMO). Although surgery was successful, severe haemodynamic instability developed post-operatively caused by cardiac arrhythmias and recurrent bleeding at the site of the surgical anastomosis, which finally necessitated the vaECMO implantation. In the first post-operative days, SAA level decreased significantly from almost 600 mg/L to 180 mg/L, suggesting a causal relationship between the tumour and the patient's AAA.

However, the patient's condition worsened over the next days, and repeated attempts to wean him off vaECMO were unsuccessful. Before tumourectomy was performed, exit strategies such as implantation of a ventricular assist device or heart transplantation were discussed extensively with the patient, but he explicitly rejected both options. Therefore, best supportive care was pursued, and the patient died shortly thereafter. Histology of the excised tumour confirmed CD-HV, negative for HHV8.

Discussion

We present a case of UCD causing AAA with malignant cardiac involvement. The clinical spectrum of UCD ranges from complete absence of symptoms to fulminant disease. The UCD can trigger inflammation leading to SAA deposition in various organs and eventually to AAA. Unicentric Castleman's disease-induced AAA is a rare entity. The vast majority of patients with UCD-HV-induced AAA reported to date initially presented with signs and symptoms related to renal impairment such as nephrotic syndrome, up to end stage renal disease, in combination with an inflammatory syndrome.[2–4] Our patient presented with symptoms of heart failure. In a 2018 review including patients with UCD and AAA, none had obvious heart involvement, only recently a case report concerning a patient with UCD-PC and heart involvement was published.[4,5] This highlights the novelty of this case, since our patient initially presented with normal renal function and only mild proteinuria, in combination with an elevated C-reactive protein. Furthermore, the HV subtype is only seen in a minority of cases associated with AAA, in contrast to the other subtypes[4]

The final diagnosis was delayed because endomyocardial and bone marrow biopsy were repeatedly negative for Congo red staining. The reason for this is unclear, but in this context, the fixation time of the specimen in formaldehyde must be discussed, influencing the outcome of histochemical stainings. Cases of patients with Congo-red negative AL amyloidosis are also described.[6,7] This demonstrates the importance of an extended diagnostic work-up of biopsies by immunohistology and/or mass spectrometry when there is a reasonable suspicion for the presence of amyloid deposits.

Surgical resection of a UCD tumour is the recommended therapy for eligible tumours and has been shown to improve patient outcomes.[8–10] Tumour resection normalizes SAA levels and is a causal therapy for UCD-induced AAA. Radiotherapy is possible in selected patients.[11] In case of unresectable UCD anti-IL-6 monoclonal antibody therapy, rituximab and steroids are treatment options.[10] Since the tumour was resectable and to achieve rapid reduction of SAA levels surgery was the therapy of choice in our patient.

In conclusion, we describe for the first time that heart failure may in fact be the primary and leading symptom of AAA caused by UCD-HV. This underlines the importance of a meticulous diagnostic work-up of patients presenting with a hypertrophic cardiac phenotype.

Lead author biography

Thomas Schuetz obtained his MD in 2015, and he has previously performed experimental murine studies dealing with neonatal cardiac regeneration after myocardial infarction as part of his PhD. He has a special interest in cardiac regeneration and heart failure. He is currently working as Resident at the University of Innsbruck (Austria) at the Department for Cardiology and Angiology.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Conflict of interest: None declared.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of the individual. The data will be shared on reasonable request to the corresponding author.

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