Cardiac Amyloidosis – A Heartfelt Diagnosis

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Abstract

When a patient presents at the cardiac care unit with symptoms of heart failure, the clinical workup includes multimodal imaging. In this case of a 72-year-old man, conventional radiography and echocardiography confirmed heart failure with a reduced left ventricular ejection fraction. The combination of an MRI, nuclear imaging, and a myocardial biopsy was needed to differentiate between an ischemic and non-ischemic origin of the newly diagnosed cardiomyopathy, and to identify the underlying condition.

Case information

A 72-year-old male with no history of cardiac disease presented at the cardiac care unit (CCU) in October 2022 with orthopnea and no palpitations or chest pain. Physical examination indicated a blood pressure of 140/109, and an irregular pulse of 157/min. Chest X-ray revealed limited bilateral pleural effusion and increased cardiothoracic ratio. The ECG showed de novo atrial fibrillation (AF) with normal ventricular response and diffuse low voltages. Blood tests indicated an increased NT-proBNP of 3,200 pg/mL (normal value < 450) and increased light protein chains. The patient was admitted with acute decompensated heart failure and treated with intravenous diuretics. Transthoracic echocardiography (TTE) during hospitalization revealed a reduced left ventricular ejection fraction (LVEF) of 30 – 35%, moderate mitral valve regurgitation, no thickening of the heart valves, and normal wall thickness without ventricular dilatation. Right ventricular systolic pressure was significantly elevated. After recompensation, the patient was started on heart failure medication and discharged in good clinical condition.

Eight weeks after discharge, no echocardiographic improvement was observed following the initiation of heart failure therapy, and coronary angiography was normal. Cardiac MRI was performed to further differentiate the etiology of the de novo heart failure.

This article is written in the concise Compendium Medicine style, using *bells* to outline important warning signs and clinical symptoms, *light bulbs* for interesting facts, and a *condition summary* using the first letter of each indicated step in the clinical process/patient follow-up (see the abbreviation list).

Abbreviations

ACM	Arrhythmogenic cardiomyopathy
AF	Atrial fibrillation
AL	Light chain amyloidosis
ATTR	Transthyretin amyloidosis
bSSFP	balanced steady state free precession
CA	Cardiac amyloidosis
CAG	Coronary angiography
CCU	Cardiac care unit
CM	Cardiomyopathy
CTR	Cardiothoracic ratio
D	Definition
DDx	Differential diagnosis
Dx	Diagnostics
E	Epidemiology
Et	Etiology
HFrEF	Heart failure with a reduced ejection fraction
Hx	Patient history
IV	Intravenously
LGE	Late gadolinium enhancement
OPT	Optimal pharmacological therapy
P	Prognosis
PE	Physical examination
SPECT	Single-photon emission computed tomography
Tx	Treatment
!	Watch out / don't forget

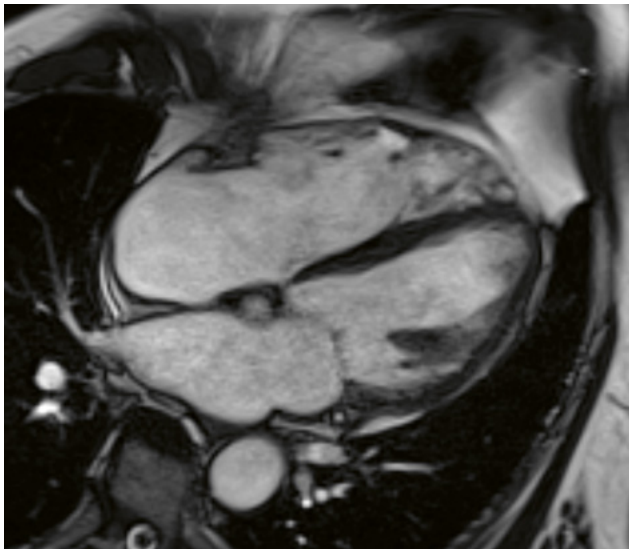
Diagnostic imaging

Cardiac MRI

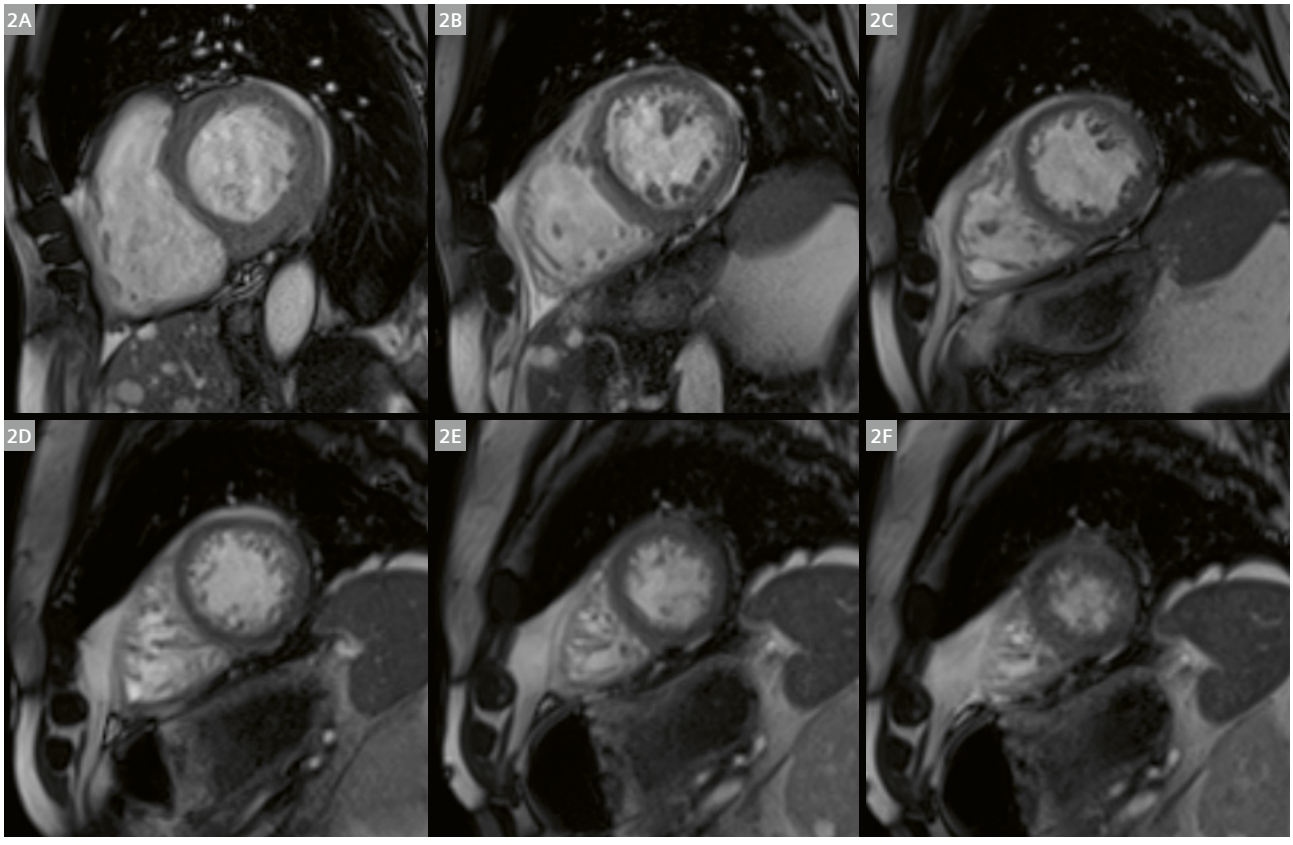
This case concerns heart failure with a reduced ejection fraction (HFrEF) based on the performed echocardiography in combination with de novo AF. An MRI with contrast was indicated to differentiate between an ischemic and non-ischemic origin of the cardiomyopathy (CM).

In January 2023, a cardiac MRI was performed. Images were acquired on a 1.5-Tesla MAGNETOM Avanto Fit (Siemens Healthineers, Erlangen, Germany). First, balanced steady state free precession (bSSFP) cine images were acquired. Then 25 mL Dotarem IV (Guerbet, Villepinte, France) was administered, and the delayed enhancement images were acquired. Both cine and late gadolinium enhancement (LGE) images were acquired in standard short-axis and long-axis views.

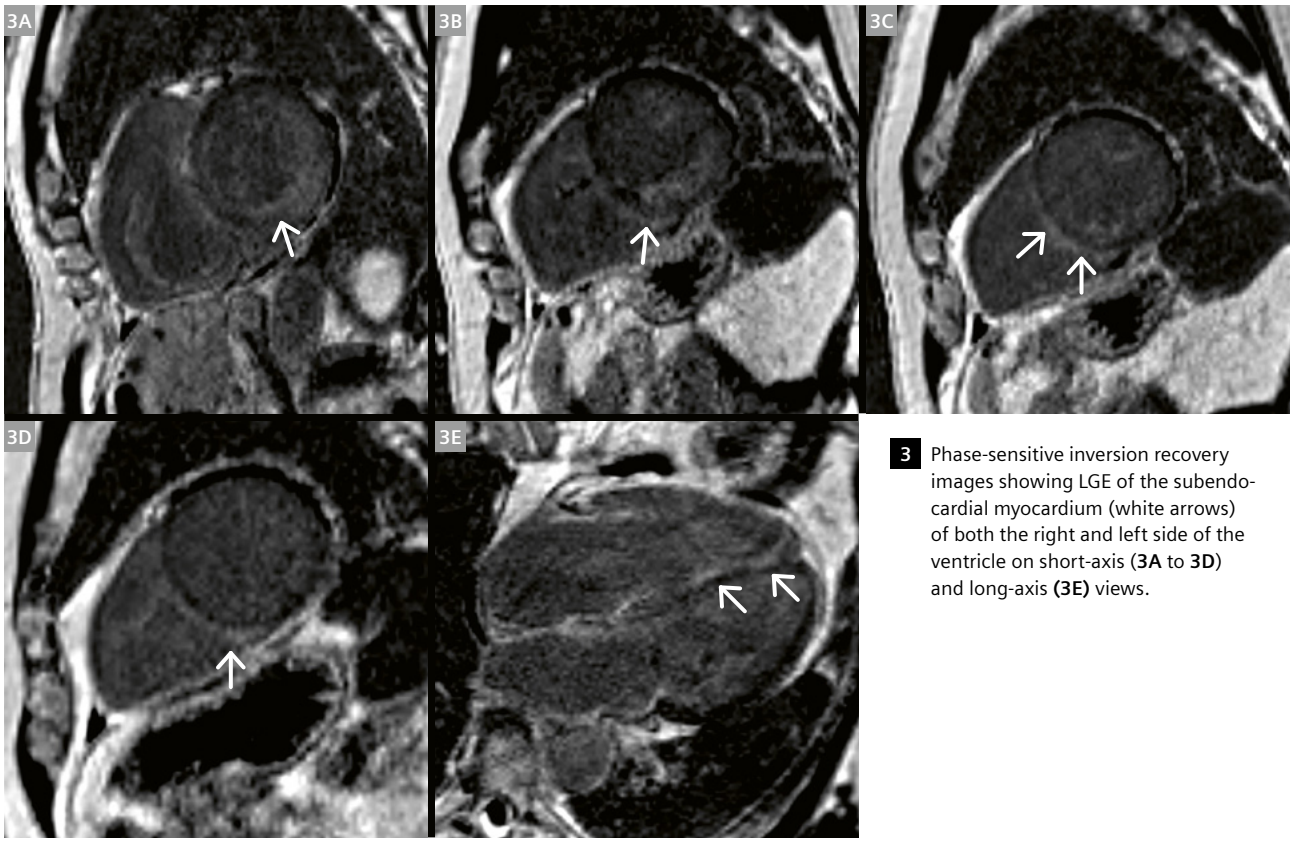
MRI confirmed a reduced LVEF of 45%. The four-chamber view (Fig. 1) revealed dilated atria, dilation of the mitral annulus, and lipomatous hypertrophy of the atrial septum. Wall movement and pericardium were normal. Apart from the mitral valve thickening, there were no evident valvular abnormalities. Administration of intravenous contrast revealed subendocardial LGE of the mid-to-apical right septal side and left side of the inferior ventricular septum, partial LGE of the papillary muscles, and LGE of the atrial wall (left more than right), see Figures 2 and 3. The pericardium was normal on both pre- and postcontrast images.



1 Four-chamber view showing dilated atria.



2 Short-axis cine series (base to apex, sagittal plane); (**2A** to **2F**) showing no focal thickening or thinning of the myocardium.



3 Phase-sensitive inversion recovery images showing LGE of the subendocardial myocardium (white arrows) of both the right and left side of the ventricle on short-axis (**3A** to **3D**) and long-axis **(3E)** views.

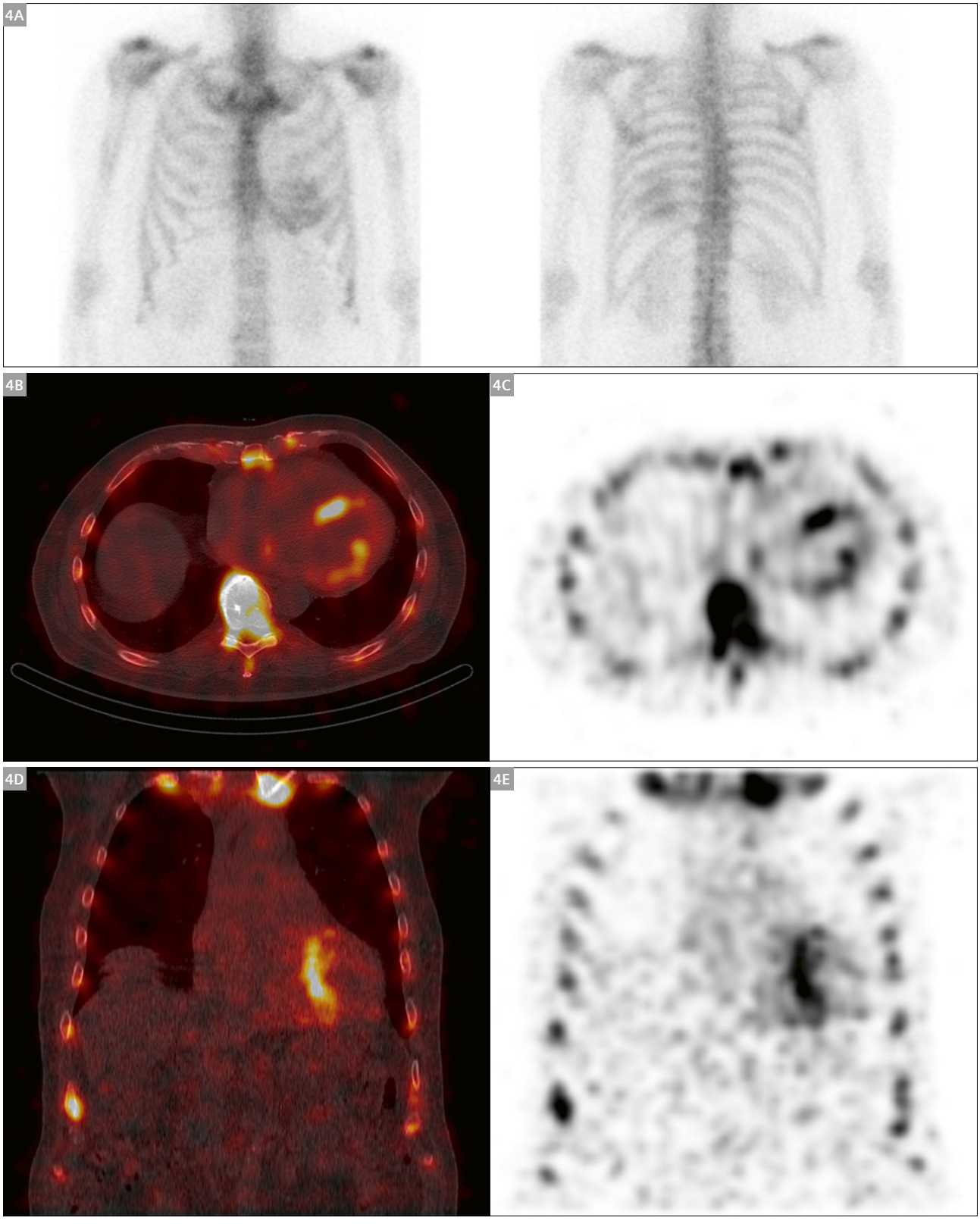
Clinical dilemma
Subendocardial enhancement may be seen in subendocardial infarction, but also in cardiac amyloidosis and systemic sclerosis. Depending on the type of findings, ischemic injury may be more or less likely. In this case, LGE not matching the coronary supply area, circular aspect, and involvement of the right side of the septum made ischemic injury less likely.

The use of contrast in MRI enables visualization of both normal myocardium and injured myocardium. Injured myocardium often shows late enhancement after 10 to 15 minutes, also known as late gadolinium enhancement (LGE). Delayed enhancement is often the result of regional differences in the extracellular volume with differences in uptake and washout due to issues such as edema, necrosis, or fibrotic tissue. The distinct pattern of LGE (e.g., subendocardial, mid-wall, or epicardial) and the location may, together with the clinical presentation, aid in defining a differential diagnosis [7].

In this case, the MRI showed subendocardial LGE. Subendocardial LGE is specifically seen in ischemic cardiac events and indicates fibrosis, as the ischemic wave front starts from the subendocardium, but can also occur in systemic sclerosis and cardiac amyloidosis [4]. The combination of extensive delayed enhancement of the septum on both the right and left ventricular side, papillary muscle, and atrial wall, not corresponding to ischemic injury or coronary infarction, increased the suspicion of amyloidosis.

Nuclear imaging
Various forms of amyloidosis can be differentiated. In instances of cardiac involvement, the predominant types are transthyretin amyloidosis (ATTR) wild type, hereditary ATTR, and light chain (AL) amyloidosis. In cases of clinically suspected cardiac ATTR amyloidosis, nuclear imaging with ^{99m}Tc-labeled bone-seeking agents is an important non-invasive diagnostic tool for confirming the diagnosis, and thereby in some cases replacing the earlier required myocardial biopsy [9]. Furthermore, myocardial uptake on bone scans can occasionally also be seen in AL amyloidosis.

Scans should be obtained 2 to 3 hours after administration of the radiotracer, and planar images or SPECT/CT of the chest are recommended. Whole-body planar can optionally be performed and can be helpful in identifying signs of systemic transthyretin amyloidosis (ATTR), e.g., uptake of the radiotracer in the shoulder and hip girdles.



4 Tc-99m-HDP SPECT:
(4A), planar bone scintigraphy anterior (left) and posterior (right) view; **(4B, 4C)** axial fusion reconstructions and scintigraphy; **(4D, 4E)**, coronal fusion reconstructions and scintigraphy.

For this patient, images were acquired on a Symbia T16 SPECT/CT (Siemens Healthineers, Hoffman Estates, IL, USA) 4 hours after administration of approximately 500 MBq ^{99m}Tc-HDP (hydroxybiphosphonate). Static planar whole-body images from anterior and posterior were acquired, as were SPECT/CT images of the thorax.

Increased uptake was seen in the wall of the left ventricle, especially in the septum and basal wall (Fig. 4). The ratio of the counts in the affected myocardium compared to the contralateral lung parenchyma on the same level was > 1.5, a finding suggestive of ATTR amyloidosis and less suggestive of AL amyloidosis [8]. Cardiac uptake can furthermore be evaluated visually and scored according to the Perugini scale, with a grade 2 or 3 for ATTR.

Perugini grading scale for cardiac amyloidosis:
- 0: no cardiac uptake, normal rib uptake
- 1: cardiac uptake < rib uptake
- 2: cardiac uptake = rib uptake
- 3: cardiac uptake > rib uptake / absent rib uptake

Case summary

This patient received an MRI to assist in the differential diagnosis for newly diagnosed heart failure and to differentiate between ischemic and non-ischemic CM. The visualized subendocardial enhancement raised suspicion of cardiac amyloidosis. The combination of the MR findings indicated the need for a bone scan for cardiac amyloidosis. The subsequent bone scan showed increased uptake in the myocardium (Perugini grade 2 or 3).

Pathophysiology

Systemic amyloidosis is characterized by extracellular deposition of insoluble amyloid fibrils. While there are many different types of amyloidosis, cardiac amyloidosis (CA) is caused in more than 95% of cases by immunoglobulin light chain amyloidosis (AL) and transthyretin-related amyloidosis (ATTR). Excessive production and malformation of antibody light chains is the cause of AL-CA, whereas ATTR involves a misfolding of the liver-derived protein transthyretin. ATTR can be hereditary or occur as wild type.

Cardiac amyloid fibril deposition leads to diffuse wall thickening, possibly mimicking hypertrophic CM, and to late gadolinium enhancement on MRI. Ventricular wall thickening results in progressive restrictive ventricular filling. LVEF can be less reliable for diagnosing CA, as low end-diastolic volumes can result in low stroke volume and thus low cardiac output while LVEF can still be preserved. Amyloid deposition primarily affects diastolic function, and additional systolic dysfunction is only seen in a late stage. The intra-atrial septum is often involved, leading to poor atrial function and predisposing the patient to atrial fibrillation. Thickening of the valvular leaflets is often associated with mild-to-moderate regurgitation. Amyloid deposition in the conduction system can lead to various conduction and bundle branch blocks. Coronary involvement usually affects small intramural vessels, leading to ischemia with normal aspects of the large coronary arteries. Pericardial effusion can be observed, but is usually limited.

Patients often present with heart failure with preserved ejection fraction (HFpEF) accompanied by exertional dyspnea or peripheral edema. General symptoms of fatigue and weakness are often attributed to advancing age. Atrial fibrillation (AF) and conduction abnormalities can be the first presentation. In particular, AF with rapid ventricular response is not well tolerated due to the restrictive filling pattern. Non-cardiac symptoms often precede cardiac involvement such as carpal tunnel syndrome (often bilaterally), spinal stenosis, neuropathy, proteinuria, and gastrointestinal symptoms.

Cardiac amyloidosis red flags
Echocardiographic concentric LV thickening without signs of high voltages on the ECG, and characteristic LGE patterns on MRI.

Case follow-up

The neurologist found no autonomous or peripheral neuropathy. Based on the MRI and SPECT scan discussed above, the patient was referred to the hematologist for further investigation of the suspected amyloidosis. A smoldering multiple myeloma was diagnosed with increased light chain proteins in the blood, but no signs of AL amyloidosis were found in the myocardial biopsy, crystal crest biopsy, or fat pad biopsy. Further immunohistochemical characterization was more suggestive of ATTR-CA, which correlates better with the findings on the bone scan. Genetic testing for hereditary ATTR showed no underlying genetic defect. The patient was therefore diagnosed with wild-type ATTR-CA and treated accordingly.

Cardiac amyloidosis

D Definition

Cardiac amyloidosis, also known as stiff heart syndrome, is a systemic infiltrative disease. It is characterized by extracellular insoluble protein deposition and is one of the leading causes of restrictive cardiomyopathy [6].

E Epidemiology

- AL subtype incidence of 1:100,000 and prevalence of 17:100,000; ATTR subtype incidence of 3.6:100,000 [10]
- ↑ due to ↑ survival and ↑ diagnostic rates

Et Etiology

- Extracellular deposition of the toxic component amyloid → ventricular wall thickness ↑ → ventricular stiffness → ventricular diastolic dysfunction
- Types of amyloidosis (1) AL amyloidosis (deposition of AL fibrils created by abnormal plasma cells, e.g., in patients with multiple myeloma), (2) wild-type ATTR amyloidosis (wtATTR, deposition of liver-produced transthyretin), (3) hereditary ATTR amyloidosis (hATTR)

Hx Patient history

Fatigue, malaise, (exertional) dyspnea, orthopnea, palpitations, chest pain, syncope, lower limb swelling, abdominal distention (ascites)

PE Physical examination

Fine lung crackles, pedal edema, jugular venous pressure ↑, ascites, orthostatic hypotension, hepatomegaly, neuropathy, periorbital purpura

DDx Differential diagnosis

Restrictive CM, cardiac hypertrophy (hypertrophic cardiomyopathy, arterial hypertension induced cardiac hypertrophy)

Dx Diagnostics

- Lab: (NT-pro)BNP ↑, Troponin T or I ↑/=, serum free light chain ↑ (AL-CA), M-protein spike on immunofixation (AL-CA)
- ECG: low voltages (no signs of hypertrophy), Q-waves early precordial leads, conduction abnormalities (AV block, bundle branch block)
- Echocardiography: LV and RV wall thickness ↑ (usually symmetric), septal wall thickness ↑, heart valve thickness ↑, ventricular dimensions =, biatrial dilatation ↑, LVEF =/↓, diastolic dysfunction, septal and lateral tissue doppler velocity ↓, longitudinal strain speckle tracking ↓, apical sparing in strain
- Cardiac MRI: native T1 mapping time ↑, LGE diffuse and subendocardial not following coronary distribution. Structural findings similar to echocardiography
- Bone scintigraphy: myocardial ^{99m}Tc-HDP uptake ↑ (ATTR-CA > AL-CA)
- Myocardial biopsy: confirmation of diagnosis and subtyping
- Fat pad biopsy: amyloid infiltration, lower sensitivity than myocardial biopsy
- Genetic analysis: differentiating wild-type and hereditary ATTR

Tx Treatment

- Patient education regarding disease and prognosis
- Pharmacological AL treatment: chemotherapy
- Pharmacological ATTR treatment: TTR synthesis inhibitors, TTR tetramer stabilizers, fibril disruptors
- Pharmacological treatment for heart failure
- Potential heart and/or liver transplantation in selected cases after good hematologic response

P Prognosis

Life expectancy
(1) AL-CA: 9 to 24 months,
(2) wtATTR amyloidosis: 5 to 7 years,
(3) hATTR 7 to 10 years

! Watch out / don't forget

- Increased risk of digoxin-toxicity in CA
- Non-dihydropyridine calcium antagonists are *contraindicated*
- Associated pathology: (bilateral) carpal tunnel syndrome, autonomous or peripheral neuropathy, spinal stenosis, nephrotic syndrome

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