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CASE REPORT
Heart failure

Chylothorax as an unusual manifestation of transthyretin cardiac amyloidosis: a case report

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Background Amyloidosis is a multi-organ disease of emerging significance in the field of cardiology. Chylothorax, a specific form of pleural effusion characterized by lymphatic fluid accumulation in the pleural cavity, is an extremely rare manifestation of amyloidosis. Notably, only five cases of chylothorax related to cardiac amyloidosis have been reported worldwide, all in amyloid light chain (AL) amyloidosis. No cases have been documented in amyloid transthyretin (ATTR) amyloidosis. Furthermore, elevated levels of serum carbohydrate antigen (CA) 125 have been associated with a poor prognosis in patients with AL cardiac amyloidosis.

Case summary We report the case of an 85-year-old Austrian man with pronounced left ventricular hypertrophy, monoclonal gammopathy, and a history of atrial fibrillation. Further examinations, including myocardial biopsy, confirmed the diagnosis of ATTR cardiac amyloidosis. A significant right-sided pleural effusion was also observed. Thoracocentesis diagnosed chylothorax, confirmed by lymphangiography. Elevated CA 125 levels were found in both serum and pleural fluid, with no other findings suspicious for malignancy. The patient underwent a short break in oral anticoagulation and received prophylactic low-molecular-weight heparin for myocardial biopsy, thoracocentesis, and lymphangiography. However, they died a few days later due to an embolic stroke.

Discussion At this time, we can only speculate about the pathomechanism of chylothorax development in the context of amyloidosis. We recommend further investigation of similar cases to deepen understanding of the underlying causes and identify potential treatment strategies. Additionally, the utility of CA 125 as a prognostic marker in ATTR amyloidosis needs further investigation.

Keywords Cardiac amyloidosis • Chylothorax • Carbohydrate antigen (CA) 125 • Case report

ESC curriculum 5.3 Atrial fibrillation • 6.3 Heart failure with preserved ejection fraction • 6.5 Cardiomyopathy

Learning points

- Chylothorax can be an unusual manifestation of amyloid transthyretin (ATTR) cardiac amyloidosis.
- High serum carbohydrate antigen 125 levels correlate with poor prognosis in amyloid light chain cardiac amyloidosis.[1] This may also be relevant for ATTR cardiac amyloidosis.

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Introduction

Amyloidosis is a multi-organ disease of emerging significance in the field of cardiology. The two main types of heart-related amyloidosis are amyloid light chain (AL) amyloidosis and amyloid transthyretin (ATTR) amyloidosis.[2]

As the number of cardiac amyloidosis diagnoses is increasing, it is clinically important to evaluate other rare manifestations of amyloidosis, more closely.

Chylothorax, a specific form of pleural effusion characterized by lymphatic fluid accumulation in the pleural cavity, is an extremely rare manifestation of amyloidosis. Triglyceride levels in the pleural fluid exceeding 110 mg/dL confirm the diagnosis of chylothorax.[3]

To the best of our knowledge, only five cases of chylothorax related to cardiac amyloidosis have been reported worldwide, all in AL amyloidosis.[4–8]

Another rare, albeit important clinical finding in AL amyloidosis was detected by Li *et al.* by demonstrating a correlation between increased serum carbohydrate antigen (CA) 125 and low overall survival in AL amyloidosis. Serum CA 125 is a tumour marker and is usually elevated in ovarian, breast, and lung cancer, leukaemia, and non-Hodgkin's lymphoma, melanoma, and gastrointestinal carcinoma, and also in infections like bacterial peritonitis and tuberculosis and in patients undergoing abdominal surgery.[1]

Summary figure

September 2022	First outpatient visit due to dyspnoea
(1 month before hospitalization)	**Medical history:** chronic atrial fibrillation; coronary heart disease; monoclonal gammopathy of undetermined significance (MGUS)
	Echocardiography: typical signs of amyloidosis
October 2022	Day of admission
Day 1	**Bone scintigraphy:** Perugini Grade 2
	Computed tomography (CT) of the chest: pleural effusion on the right side
	Serum electrophoresis and immunofixation: monoclonal overproduction of light chains IgG kappa
Day 4	**Cardiac MRI:** typical findings of cardiac amyloidosis
Day 8	**Bone marrow biopsy:** borderline values between MGUS and smouldering myeloma
	Myocardial biopsy: only findings of ATTR amyloid
Day 10	**Thoracentesis on the right side:** 2000 mL milky yellow liquid, findings of an exudate—chylothorax (triglycerides 2383.9 mg/dL); increased CA 125
	Post-puncture pneumothorax—conservative
Day 16	**Positron emission tomography-CT:** no findings of a tumour disorder
Day 22	**Angiography of the lymphatic vessels** with ethiodized oil as contrast media: chylothorax is confirmed
Day 23	Progressive confusion, tetraplegia
	Head MRI inclusive angiography: multiple microinfarcts frontal, high parietal, and occipital on both sides
	Transfer to a neurologic department
Day 32	Death due to stroke

Case presentation

An 85-year-old Austrian male patient is admitted for further evaluation to our cardiology department with a suspected diagnosis of cardiac amyloidosis. The patient presents with increasing exertional dyspnoea, classified as New York Heart Association (NYHA) Class II. His cardiac history includes coronary heart disease, persistent atrial fibrillation, and arterial hypertension.

Additionally, the patient suffers from monoclonal gammopathy of undetermined significance (MGUS). This has been monitored by regular laboratory controls; therapy of MGUS, however, has not been considered indicated so far.

Furthermore, a papillary renal cell carcinoma on the right side was fully removed in 2008, followed by the removal of an oncocytoma from the left kidney in 2013.

Physical examination shows bilateral leg oedema. Auscultation of the lungs reveals a weakened breath sound on the right basal side, while auscultation of the heart is without pathologic findings.

Echocardiography reveals significant left ventricular hypertrophy with a septal thickness of 18 mm, a preserved left ventricular systolic function, but severe diastolic dysfunction, and pericardial effusion. Additionally, echocardiography shows granular sparkling texture and strain analysis indicates 'apical sparing' (*Figure 1A* and *B*).

The bone scintigraphy (technetium-99m-diphosphono-1,2-propandicarbonacid scan) demonstrates increased tracer storage in the myocardium, according to Perugini Grade II (*Figure 2*).

Cardiovascular magnetic resonance-based native T1 mapping reveals prolonged relaxation time; after the application of contrast media, we detect diffuse late gadolinium enhancement in the myocardium of both ventricles supporting suspicion of amyloidosis.

Additionally, the patient has been demonstrating monoclonal gammopathy with increased kappa-free light chains for years, necessitating a myocardial biopsy to determine amyloidosis type.

The histological examination exclusively identifies ATTR amyloid, confirming the diagnosis of ATTR cardiac amyloidosis. Thus, the patient qualifies for tafamidis therapy but not chemotherapy (*Figure 3A–C*).

In addition, a bone marrow biopsy is performed showing a borderline finding between MGUS and smouldering myeloma. Amyloid is also identified, but exclusively ATTR amyloid, not AL amyloid. Upon admission, a significant right-sided pleural effusion is observed (*Figure 4*).

Despite forced diuresis with furosemide, thoracentesis is performed due to no improvement, yielding 2000 mL of milky yellow fluid. Post-aspiration, the patient developed a pneumothorax, which was managed conservatively. Lab analysis reveals a tumour-free pleural effusion with elevated triglycerides (2383.9 mg/dL, upper limit 110 mg/dL) indicative of chylothorax.

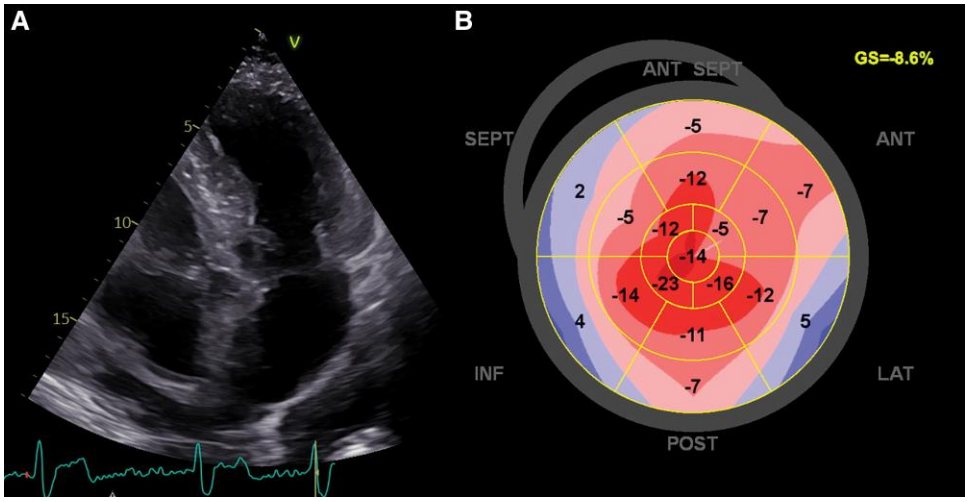

Figure 1 (*A*) Four-chamber view showing pronounced left ventricle hypertrophy. (*B*) Strain analysis with apical sparing.

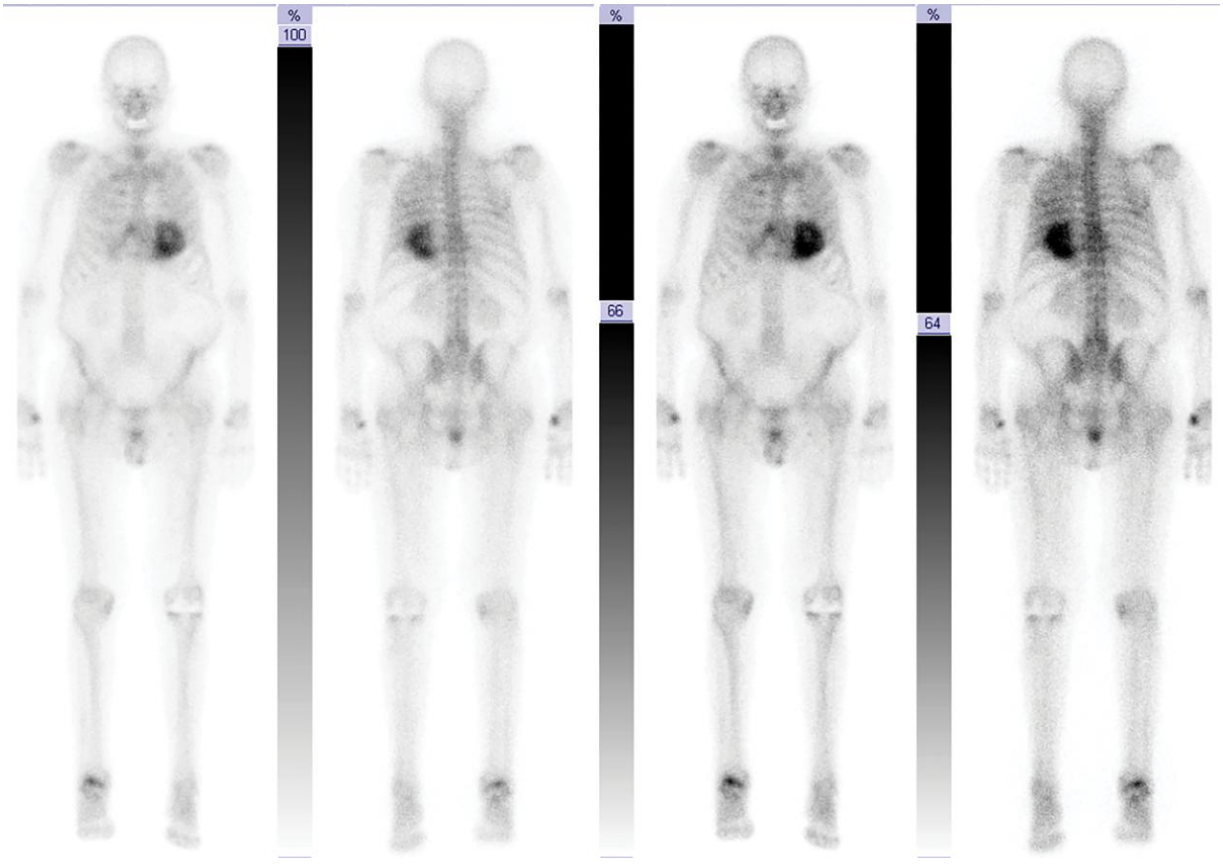

Figure 2 Perugini Grade II in the technetium-99m-diphosphono-1,2-propandicarbonacid scan.

Given the initial suspicion of a malignant origin for the pleural effusion, tumour markers were assessed in both serum and pleural fluid indicating an elevated CA 125 level (2806.3 U/mL, upper limit 35 U/mL).

The subsequent positron emission tomography-computed tomography scan shows no evidence of suspicious tumours. To further investigate the pleural effusion, a lymphangiography is conducted. Ethiodized oil is administered as a contrast agent into the lymphatic vessels through the inguinal lymph nodes on both sides (10 mL each). Approximately 20 min later, a leak is observed in the right lung, confirming the diagnosis of chylothorax (*Figure 5*).

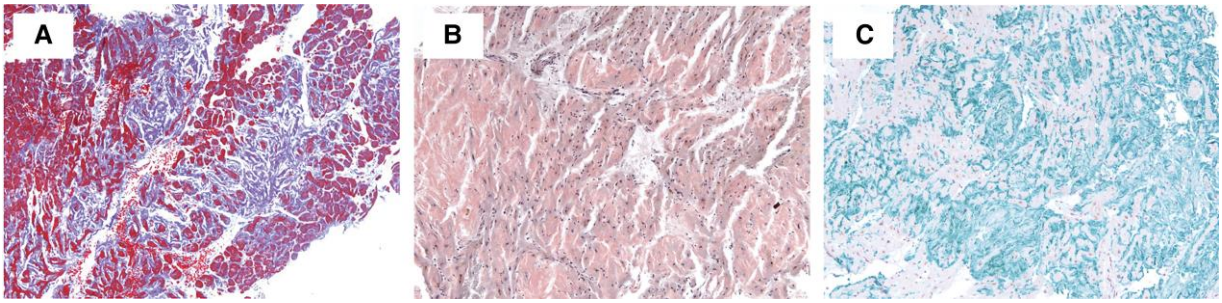

Figure 3 (*A*) Masson trichrome staining of the myocardium, amyloid purple. (*B*) Congo red staining of the myocardium, amyloid red. (*C*) Immunohistochemical detection of transthyretin in myocardium.

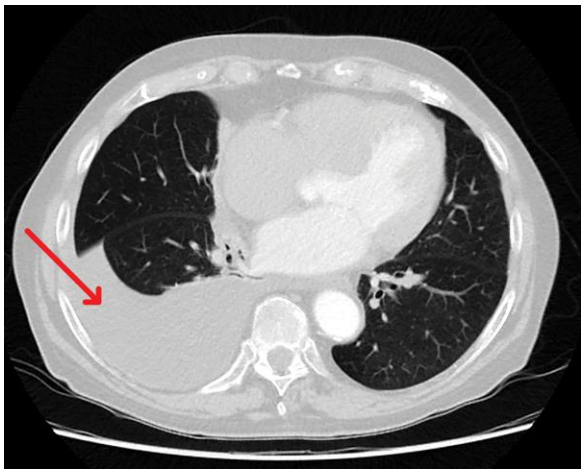

Figure 4 Computed tomography chest with a pleural effusion on the right side.

The patient's oral anticoagulation is temporarily interrupted and replaced with a prophylactic dose of low-molecular-weight heparin to allow myocardial biopsy, thoracocentesis, and lymphangiography.

A day after lymphangiography, the patient develops increasing confusion and tetraplegia, and a subsequent head magnetic resonance imaging (MRI) with angiography reveals multiple infarction areas. The patient is transferred to a neurological department. However, the patient died 9 days later due to an embolic stroke.

Discussion

Here, we describe the course patient with ATTR cardiac amyloidosis and unusual clinical findings.

Chylothorax is an exceptionally rare occurrence typically linked to surgery, trauma, or malignant diseases like chronic lymphocytic leukaemia, Kaposi syndrome, lung carcinoma, lymphoma, or metastatic malignancy.[3]

To our knowledge, five case reports currently describe chylothorax in connection with cardiac amyloidosis. Each of these patients had AL amyloidosis.[4–8]

In our case, we present the first patient with chylothorax in connection with ATTR cardiac amyloidosis.

Our patient's medical history includes a monoclonal gammopathy, in which only ATTR amyloid, not AL amyloid, is detected.

At this time, we can only speculate about the pathomechanism of chylothorax development in the context of amyloidosis.

In the case report by Patel *et al.*[4] in May 2022, pleural and pericardium AL amyloid accumulation was found after histological examination.

In September 2003, Berk *et al.* published a study examining 636 AL amyloidosis patients, detecting 35 with persistent pleural effusion. No echocardiographic and renal function differences were observed between those with and without chylothorax. The authors suggested pleural amyloid infiltration played the key role.[9]

We suspect amyloid infiltration in our patients' pleura and lymphatic vessels, as the cause of right lung lymphatic fluid leakage.

Another interesting finding was elevated CA 125 in serum and pleural fluid without evidence of malignancy.

The study of Li *et al.*[1] correlates increased serum CA 125 with low overall survival in AL cardiac amyloidosis. We speculate that CA 125 could also be a prognostic predictor in ATTR cardiac amyloidosis.

Our case promotes three points:

First is describing the first documented ATTR cardiac amyloidosis patient with chylothorax. While we cannot fully explain the pathomechanism, exploring its genesis in similar cases is recommended to gain more information and improve interventions.

Second, high serum CA 125 values predict low overall survival in AL cardiac amyloidosis. Research is needed to determine its association with ATTR cardiac amyloidosis.

Lastly, despite monoclonal gammopathy, multiple myeloma, or Waldenstrom's disease, exploring amyloidosis type is vital due to different therapeutic consequences. Our patient qualifies for Tafamidis therapy as only ATTR amyloid is detected.

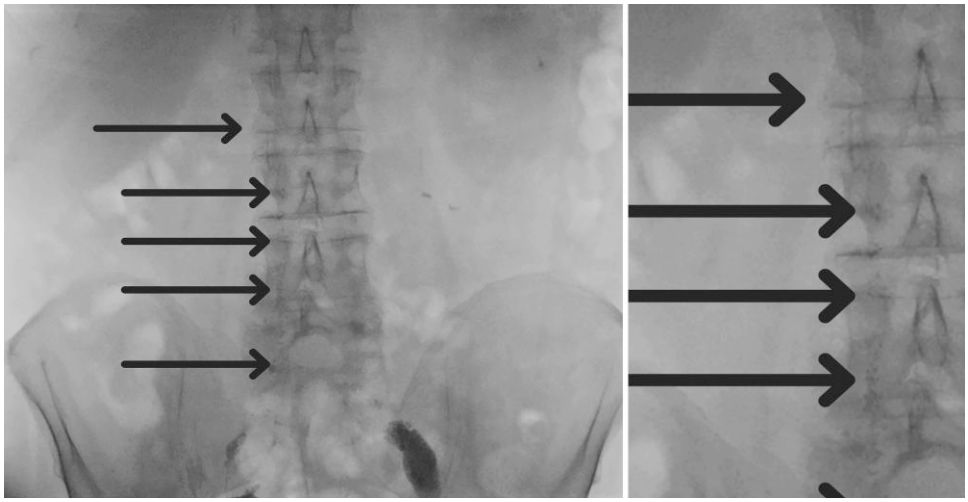

Figure 5 Lymphangiography with ethiodized oil, which leaks in the shape of small balls in the right lung.

Lead author biography

Dr. Christina Pöschl earned her Diploma in Human Medicine from the Medical University of Vienna, Austria, in 2016. She completed her general physician training at Rohrbach Hospital and Ordensklinikum Elisabethinen Linz by 2020 and began her specialization in internal medicine and cardiology at the Ordensklinikum Elisabethinen Linz later that year. In January 2022, she obtained an emergency medicine diploma, underscoring her dedication to advancing her clinical expertise and delivering exceptional patient care.

Supplementary material

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

Consent: Informed consent has been obtained from the patient's relatives for the publication of their anonymized data, ensuring that all aspects of the case report comply with the COPE standards.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data supporting the findings of this case report are available within the manuscript and its supplementary materials. Additional data are available from the corresponding author upon reasonable request.

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