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Case Report

Concurrent Amyloid Light-Chain Cardiac Amyloidosis and Abdominal Leiomyosarcoma-Diagnostic and Therapeutic Challenges

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Abstract

Diagnosis of cardiac amyloidosis is challenging due to its insidious nature and low incidence. It requires a high degree of clinical suspicion and is typically pursued once all other etiologies for heart failure are excluded. Similarly, metastatic leiomyosarcoma is a rare type of soft tissue cancer, usually associated with an aggressive course. We present for the first time, to our knowledge, a case of a 66-year-old male with concurrent development of amyloid light-chain (AL) cardiac amyloidosis-related heart failure and metastatic abdominal leiomyosarcoma. This case depicts the complex simultaneous diagnosis of both rare diseases, as well as the dilemma of administrating anthracycline-based therapy, the preferable therapy for leiomyosarcoma, in the presence of infiltrative toxic cardiomyopathy and heart failure.

Keywords: Amyloidosis; Leiomyosarcoma; Heart Failure; Anthracycline; Cardiotoxicity; Cardio-Oncology

Case Description

A 66-year-old male with a history of hypertension and hypothyroidism was referred to stress echocardiography as part of the evaluation of new-onset bilateral leg enema. Initial resting echocardiography revealed a preserved left ventricle ejection fraction (LVEF) of 55%, with moderately reduced right ventricle (RV) function and elevated systolic pulmonary artery pressure (SPAP) of 53 mmHg. During the stress test, the patient developed rapid atrial fibrillation (AF) and underwent electrical cardioversion, with resultant failure to preserve sinus rhythm. Five months later the patient was readmitted due to chest pain and dyspnoea in the presence of increased troponin levels. Electrocardiogram (ECG) showed normal sinus rhythm (75 beats per minute) with right

bundle branch block (RBBB) and 1st-degree atrioventricular block. The ECG's voltage was normal, with no signs of ischemia (Figure 1). Echocardiography demonstrated mild segmental defect with a LVEF of 50%, mild LV hypertrophy with an interventricular septum (IVS) of 13mm, grade 2 diastolic dysfunction with increased E/A ratio and decreased deceleration time (Figure 2), mildly dilated right ventricle and moderate pulmonary hypertension of 51mmHg. The patient was then referred for coronary angiography, which revealed angiographically normal coronary arteries, and the diagnosis remained unclear. Based on the patient's symptoms of heart failure, angina, elevated troponin levels, paroxysmal AF, increased IVS, and diastolic dysfunction; all in the absence of coronary disease, a suspicion for infiltrative cardiomyopathy was raised. A pyrophosphate nuclear scintigraphy was performed, excluding transthyretin–related amyloidosis. Endomyocardial biopsy showed perivascular depositions of eosinophilic amorphous hyaline material, which stained positively to Congo red staining, representing amyloid deposits. Further blood work revealed a monoclonal lambda spike with increased free light chain levels in the blood (1400 MG/L) and a reduced Kappa/Lambda ratio of 0.01. Bone marrow biopsy showed infiltration with 11% monoclonal plasma cells. Congo red stain was negative. According to the symptoms, cardiac biomarkers and endomyocardial biopsy, the patient was diagnosed with cardiac amyloid light-chain (AL) amyloidosis. Troponin and Pro-Brain natriuretic peptide (Pro-BNP) (10355pg/ml) were both elevated; compatible with rMAYO score 4 [1]. Due to suspicious lung nodules found during the nuclear scintigraphy scan, the patient underwent a Positron Emission Tomography-Computed Tomography (PET-CT) that demonstrated an abdominal mass with lesions suspicions for metastases to the liver and lungs. Biopsy taken from the abdominal mass confirmed the diagnosis of leiomyosarcoma (LMS). The patient was thus simultaneously diagnosed with primary AL amyloidosis and metastatic LMS. While the preferred therapy for LMS is an anthracycline-based regimen, it is risky to administer in this setting due to its cardio toxic potential [2], and data is limited regarding the use of anthracyclines in grade 4 cardiac AL amyloidosis patients. Following a multidisciplinary Concilium of Haematologist, Oncologist and Cardiologist, the patient was initiated with a protocol therapy of bortezomib for his cardiac AL amyloidosis and gemcitabine and paclitaxel for his LMS. Due to symptomatic heart failure (HF), consistent with New York Heart Association III, spironolactone and furosemide were initiated. At that time point, the patient was treated with 2 cycles of bortezomib (1.3 mg/m^2, once weekly) followed by 2 cycles of daratumumab (16 mg/kg), administered in combination with doxycycline 100 mg twice a day, and 2 courses of gemcitabine (1000 mg/m2 given on days 1 and 8 every 21 days) and paclitaxel (175 mg/m2 on day 8 every 21 days). At a 30-day assessment, following the initiation of protocol therapy, a gradual decrease in Lambda levels was observed (Table 1). Follow-up CT showed a right abdominal mass (9.6*9.2cm) with multiple metastases to the liver and lungs (Figure 3). Two days following daratumumab therapy and 8 days following gemcitabine therapy, with an overall 37 days from the initiation of therapy, the patient was referred to the emergency room due to diarrhea and a mechanical fall. While waiting in the emergency room, the patient lost consciousness and cardiopulmonary resuscitation was initiated. Initial blood tests later revealed pancytopenia, acute on chronic renal failure, elevated troponin and BNP, and elevated C-reactive protein (Table 1). Despite appropriate resuscitative efforts, the patient passed away.

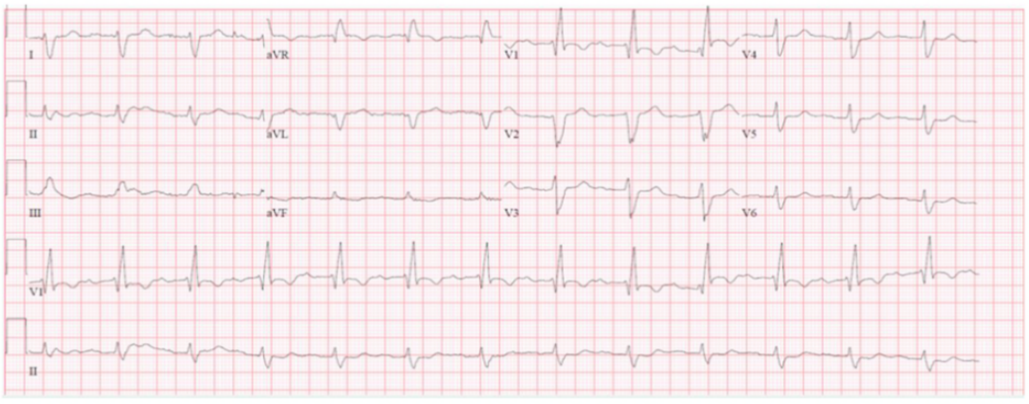

Figure 1: Electrocardiogram performed on patient's index presentation.

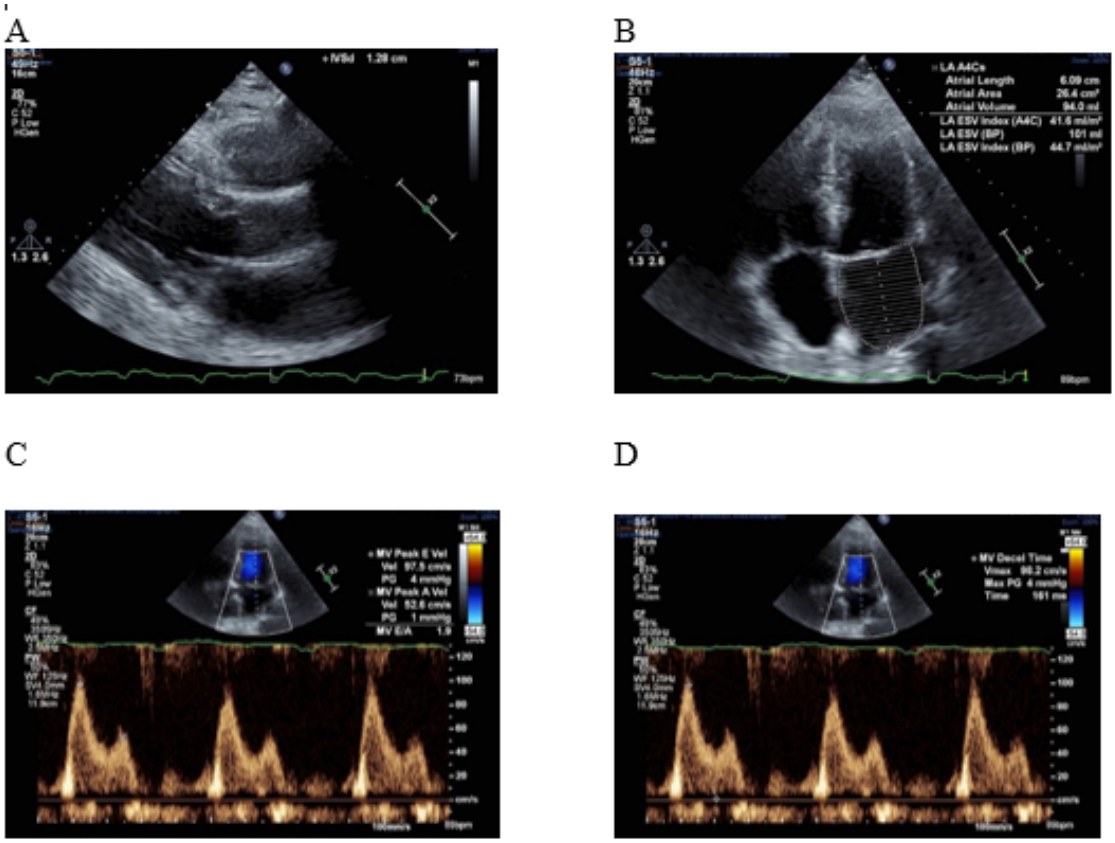

Figure 2: Echocardiography images showing diastolic dysfunction with a restrictive pattern with an elevated E/A ratio and decreased deceleration time (DT). A Mild left ventricle (LV) hypertrophy with an interventricular septum (IVS) of 13mm B Dilated left atrial (LA) with elevated LA volume index C Elevated E/A ratio D Decreased DT.

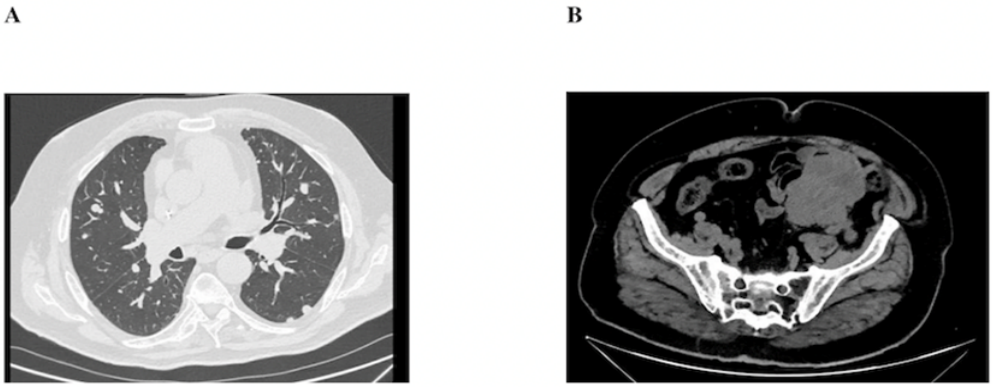

Figure 3: Computed tomography. A Multiple bilateral lung metastases B Pelvic mass, displacing small bowel intestine.

	Pre-treatment	2nd therapy	3rd therapy	4th therapy
BNP (PG/ML)	975	1065	515	
Troponin I (ng/L)	403		309	266
Hemoglobin (q/dL)	11	11.7	10.2	11.5
WBC (10e3/mcqL)	8.7	42	38.8	7.2
Platelets (10e3/mcqL)	262	224	267	338
Creatinine (mg/dL)	1.15	1.45	1.54	1.37
Kappa (MG/L)	19.6	15.3		21.4
Lamda (MG/L)	1400	931		863
Kappa/Lambda ratio	0.01	0.02		0.02
BNP= Brain natriuretic peptide, WBC=Wight Blood Cells				

Table 1: Blood tests.

Discussion

AL amyloidosis is a rare disorder caused by a small B-cell clone, usually plasma cell, synthesizing an unstable misfolded light chain, which is prone to form amyloid fibrils that infiltrate involved organs. The heart is the most common site of involvement (around 75% of cases), resulting in infiltrative cardiomyopathy, leading to fatal progressive heart failure and cardiac arrhythmias [3]. Cardiac AL amyloidosis is considered a rare disease, with an incidence of 9.7 to 14 cases per million person-years [4]. The median survival for patients with AL amyloidosis without treatment is around 9 months with cardiac involvement showing an inverse relationship to survival [5]. Treatment is usually based on bortezomib- dexamethasone [6], followed by autologous stem cell transplantation in selected patients. Until recently, patients with progressive cardiac involvement had a poor prognosis, with median overall survival of 6 months for patients with rMAYO score of 4, despite treatment [7]. In 2021, the introduction of daratumumab (anti CD 38 monoclonal antibody) based combination therapy showed high rates of hematologic and cardiac responses giving hope for improved outcomes even for advanced-stage disease [8]. Abdominal LMS is also a rare and aggressive cancer. In concordance with other soft tissue tumours, LMS incidence increases with age and its prognosis is related to the histologic grade, tumour size, and tumour stage. The preferable treatment in a patient with metastatic LMS is based on anthracyclines with a response rate of 10-25% [9]. However, as mentioned previously, anthracyclines are infamously known for their cardio toxic side effect profile [2]. Patients who are at risk for developing cardiotoxicity or are already with symptomatic HF should avoid this type of therapy as their clinical status is already quite tenuous and would not benefit from any more insult to the myocardium. Thus, our clinical dilemma presented itself as we were faced with the decision of whether to use first-line optimal therapy for this patient's LMS and further exacerbate their HF, or attempt to treat his aggressive soft tissue tumour with alternative therapeutic agents. This is the first case report, to our knowledge, to present a patient with concurrent AL cardiac amyloidosis and abdominal LMS. When re-evaluating our patient, there appear to be multiple signs relating to cardiac amyloidosis such as the new onset of atrial fibrillation resistant to cardioversion, concentric hypertrophy by echocardiography, and elevated serum Pro-BNP and troponin. Typical associated signs and symptoms of cardiac amyloidosis are due to the infiltrative misfolded protein deposition that results in constrictive cardiomyopathy and include signs of right-sided HF such as lower extremity enema, ascites, dyspnoea, and hepatic congestion. Other key features include arrhythmia (AF) and conduction disorders (RBBB), which have been thought to stem from the disruption of the conduction system from misfolded protein deposition. Relevant biomarkers for diagnosing and monitoring disease include cardiac troponin and Pro-BNP, and their serum levels correlate with prognosis [10]. Another typical finding, which was not present in our patient, is the presence of low-voltage ECG in the setting of left ventricular hypertrophy [10]. Ultimately, after a prolonged multi-disciplinary discussion with our hospital's experts in Oncology, Hematology, and Cardio-oncology, the decision was made to avoid anthracycline therapy due to its high potential to produce a cardiotoxic effect in symptomatic HF patients, in the face of limited to no data published in AL cardiac amyloidosis patients. Daratumumab was added shortly after initiation of therapy in an attempt to achieve a fast reduction of serum light chain and potentially decrease direct cardiotoxicity. Both AL cardiac amyloidosis and LMS are in and of themselves rare diseases that act as challenging diagnoses for clinicians, nonetheless presenting in the same patient. Cardiac amyloidosis represents a small incidence of patients who develop restrictive cardiomyopathy and HF and is a challenging diagnosis

due to its insidious nature. It requires a high degree of clinical suspicion and is typically only pursued once all other etiologies of HF are explored. This case represents the difficulties and delays in diagnosing cardiac amyloidosis, and emphasize the need for high clinical suspicious. Furthermore, it introduces for the first time a concurrent diagnosis of abdominal LMS, which challenges the treatment protocol for those two rare diseases.

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