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Case Report

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A Rare Case of Cardiac Amyloidosis Secondary to Multiple Myeloma in A Young Male Presenting with Shortness of Breath

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ABSTRACT

Introduction: Multiple myeloma (MM) is a haematological malignancy associated with various systemic manifestations, including AL amyloidosis.AL amyloidosis is a systemic condition arising from abnormal protein misfolding and deposition, leading to organ dysfunction. Cardiorenal involvement is characteristic. Cardiac amyloidosis causes significant morbidity and mortality, particularly in MM patients.

Case Report: A 40-year-old previously well male presented with exertional dyspnoea, lower limb swelling, and frothy urine. Clinical examination and investigations were consistent with an MM complicated by AL amyloidosis affecting the heart and kidneys. The diagnosis of amyloidosis was confirmed through renal biopsies revealing Congo red positivity, along with cardiac imaging showing typical amyloidosis findings. The presence of bone marrow plasma cells 72% confirmed myeloma.

Conclusion: This case highlights the challenges in managing MM-associated AL amyloidosis with cardiac and renal involvement. It underscores the importance of comprehensive diagnostic approaches, multidisciplinary collaboration, and tailored treatment strategies. Despite the poor prognosis, diligent management can lead to favourable outcomes and improved quality of life for affected individuals.

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Introduction

Multiple myeloma (MM) is a haematological malignancy resulting in dysfunction across various organs due to the abnormal growth of plasma cells producing monoclonal proteins. Its hallmark features include bone marrow infiltration by these plasma cells, overproduction of monoclonal proteins (either light or heavy chains) and compromised immune function [1]. Almost half of the multiple myeloma patients experience renal complications, with cast nephropathy, monoclonal immunoglobulin deposition disease (MIDD), and light chain (AL) amyloidosis being the primary causes of renal injury mediated by monoclonal immunoglobulins. Additionally, cardiac involvement is prevalent in multiple myeloma, often presenting as restrictive cardiomyopathy due to the deposition of light chains or amyloid [2].

Amyloidosis is a rare systemic condition characterised by the deposition of abnormally folded low molecular weight protein subunits in beta-pleated configuration in various extracellular tissues. These fibrils are insoluble and resistant to degradation [1,3]. There are various types of amyloidosis [3]. The commonest form, immunoglobulin light chain (AL) amyloidosis, occurs when immunoglobulin light chains or their fragments are deposited [4]. The AL amyloidosis is associated with multiple myeloma, MGUS and B cell dyscrasia [4].

Cardiac amyloidosis is a myocardial pathology characterised by the extracellular deposition of amyloid fibrils throughout the myocardium [5]. Two main types are affecting the heart: ATTR and AL amyloidosis. ATTR can be acquired or hereditary [7]. Acquired form is the most common form worldwide [5]. This infiltration process causes biventricular hypertrophy, which leads to concentric ventricular remodelling and reduces cardiac output [1].

Here, we present a case of a 40-year-old male with cardiorenal syndrome due to AL amyloidosis with background multiple myeloma diagnosed concomitantly.

Case Report

A previously healthy, 40-year-old male driver had shortness of breath on exertion and swelling in both lower legs for one-month duration. His exertional dyspnoea gradually worsened over time. Initially, it occurred on moderate exertion, but later, he was short of breath while on mild exertion. The lower limb swelling initially started at the ankles and then extended to the calves, eventually leading to Generalized edema. Later, the patient developed orthopnoea but denied any chest pains or palpitations. He also reported intermittent frothy urine but denied any presence of blood in the urine or decreased urine output. The patient also reported loss of appetite, fatigue, malaise, and lethargy, although there has been no significant weight loss. He did not have any history of backache, constipation, polyuria or polydipsia, bone pains, or sensorymotor weakness. Additionally, he denied experiencing joint pains, alopecia, or photosensitive rash. Furthermore, the patient denied any unsafe sexual practices, recent drug intake, or toxin exposure.

During examination, the patient was found to have mild pallor and facial puffiness. There was no lymphadenopathy. Lower limb pitting oedema was observed up to the knee level. Cardiovascular examination showed elevated jugular venous pressure (JVP) and a pulse rate of 96 beats per minute with a good volume pulse. Blood pressure was 100/60 mmHg, with no postural drop. A dual rhythm was noted without any murmurs on auscultation. A respiratory system examination revealed a respiratory rate of 16 breaths per minute, bibasal crepitations, and reduced air entry. Abdominal examination showed mild distension, with flank dullness. No Organomegaly Neurological Examination Yielded Normal Findings

The results of the investigations are summarised in Table 1. Laboratory tests showed severe hypoalbuminemia and significant proteinuria in the nephrotic range. The spot urinary protein creatinine ratio was notably elevated at 4614mg/g. ESR levels were high, with anaemia and a moderate rouleaux formation. Electrocardiography showed distinct features, including a low voltage QRS complex, q in V1-V3, and t inversion in V4-V6. (Figure 1a). Transthoracic echocardiography confirmed the presence of concentric hypertrophy of the left ventricle, interventricular septal hypertrophy with a speckled appearance, reduced ventricular cavity size, biatrial enlargement, and pericardial effusion. There were no regional wall motion abnormalities. The ejection fraction was 50-55%, which is characteristic of cardiac amyloidosis (Figure 1B-D) Collectively, these findings strongly suggest the presence of heart failure with preserved ejection fraction and nephrotic range proteinuria associated with amyloidosis with cardiorenal involvement.

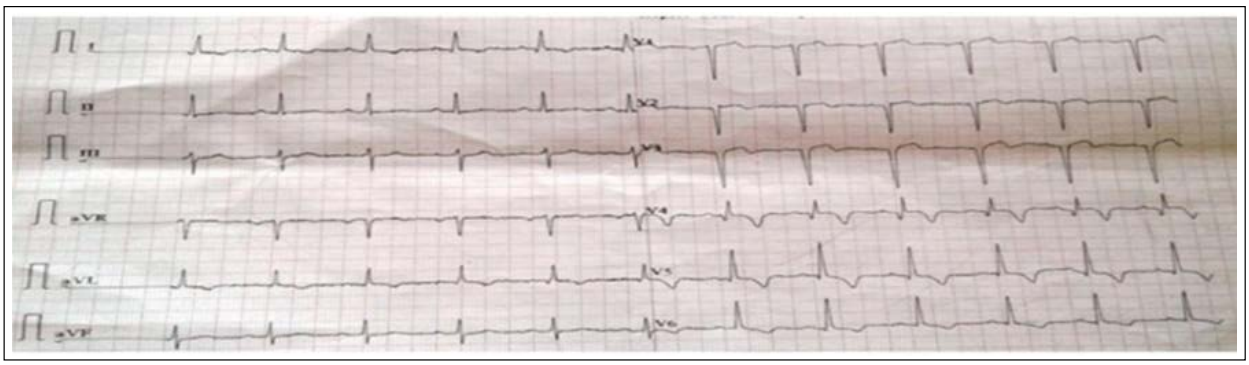

Figure 1A: Shows ecg of q waves in v1-v3 and t inversion in v4-v6

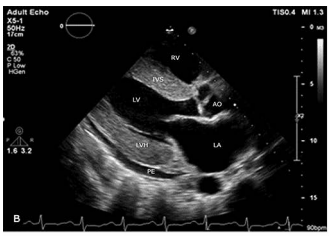

Figure 1B: Showing pericardial effusion and left ventricular hypertrophy in the parasternal long axis view

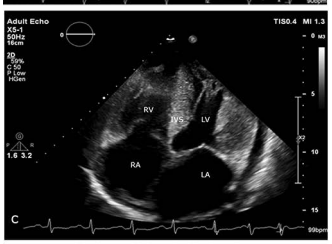

Figure 1C: Showing small ventricular cavity size, biatrial enlargement.and interventricular septal hypertrophy with a speckled pattern in apical four chambers view

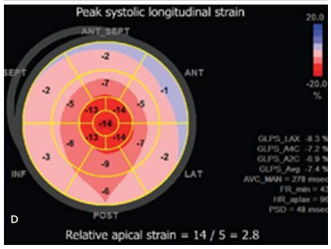

Figure 1D: Showing global reduction of longitudinal strain and relative apical sparing of longitudinal strain was seen

Serum and urine protein electrophoresis tests were done to investigate suspected dysproteinemia. The results showed a clear monoclonal band in the gamma region with background immunoparesis. The level of the M band was measured at 26.8g/l, and urine protein electrophoresis yielded negative results for Bence Jones protein. Additionally, the serum-free light chain assay revealed a K/L ratio of 0.016. Immunofixation electrophoresis detected Ig G lambda light chain paraproteins. A subsequent bone marrow biopsy confirmed a significant presence of monoclonal plasma cells, comprising 72% of the bone marrow monoclonal plasma cells. The above findings confirmed plasma cell myeloma. However, Serum calcium was not high, and no lytic lesions were observed in the skeletal survey. According to the International Staging System for myeloma, the measured beta-two microglobulin level of 8.15 mg/l, LDH 494 IU/L indicates RISS stage 3 symptomatic myeloma. A renal biopsy was performed, and results showed the presence of pale pink, acellular, glassy amyloid deposits, which were visible with H&E staining. Salmon pink staining was also shown with Congo red (Figure 2A-2C). These deposits showed positive apple green birefringence under polarised light, confirming the diagnosis of renal amyloidosis.

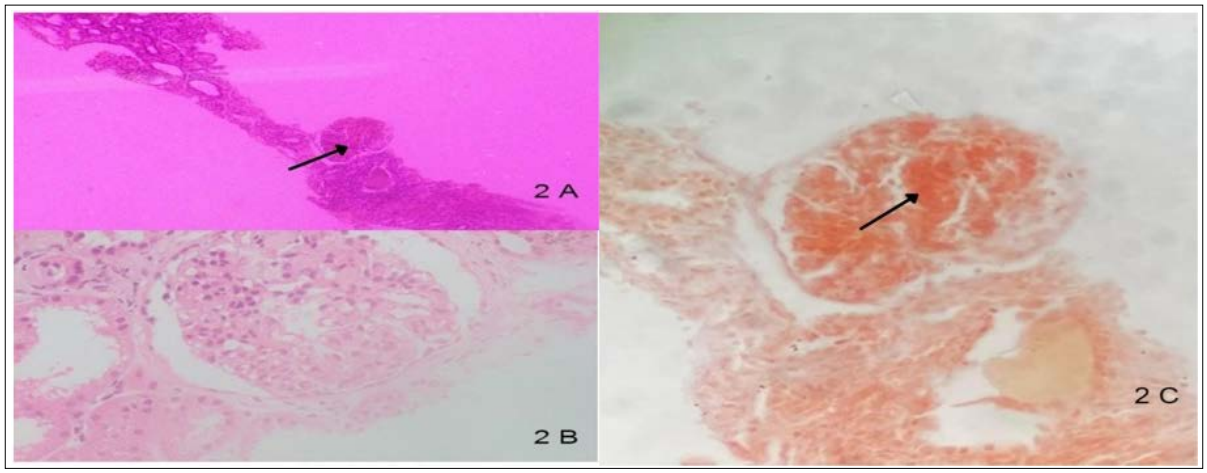

Figure 2A&B: Show under Light microscopy,the renal biopsied specimen revealed viable glomeruli and mesangial hypercellularity with mesangial matrix expansion with the presence of pale pink,acellular ,glassy amyloid deposits.

Figure 2C: Illustrates the presence of distinctive salmon pink staining, indicative of amyloid deposits, as observed under congo red staining

Table 1

Investigations	values	Reference range
WBC	9.17	4000-10 000/µl
HB	9.7	13.2-16.5g/dl
PLT	181	150 000-450000//µl
BLOOD PICTURE	Moderate anemia compatible with anemia of chronic disease. No overt evidence of plasma cell dyscrasias, moderate rouleaux formation	
AST	17	0-35U/L
ALT	13	0-40U/L
T. PROTEIN	6.7	6-8.5 g/dl
ALBUMIN	1.4	3.5-5.3g/dl
GLOBULIN	5.3	3.5-5.1g/dl
T-BIL	5.7	5-19 µmol/l
D.BIL	3.0	0-5 µmol/l
I.BIL	2.7	
S. ALP	65	0-120U/L
PT/INR	0.99	0.8-1.1
APTT	35	30-40 s
ANA	Negative	
ds DNA	Negative	

C3 **C4**	70 26	83-177mg/dl 12-36mg/dl
CRP	<0.5	0-5mg/l
ESRmm/hr	110	<20mm/hour
S. CREATININE	130	70-115 /µmol/l
BLOOD UREA	27	5-20mg/dl
URIC ACID	7.9	4-8.5 mg/dl
SODIUM **POTASSIUM** **CALCIUM** **PHOSPHATE**	136 4 1.8 1.3	135-145 mmol/l 3.5-5 mmol/l 2.2-2.7 mmol/l 1.12-1.45mmol/
ECG	q in v1-v3 and T inversions in v4-v6	
TROPONIN I	128	0-12ng/l
CXR- PA	marginally enlarged heart, but no Kerley B lines, no upper lobe diversion, mild obliteration of costophrenic angle	
Sputum AFB	3 early morning samples negative	
UFR	protein-3+, pus cells- occasional, red cells3-5	
Urine dysmorphic red cells	negative	
UPCR	4614	<200 mg/g
Uss abdomen	B/L acute renal parenchymal changes, mild to moderate ascites, B/L pleural effusion	
2D ECHO	hypertensive heart disease, EF55-60%, No RWMA	
FBS	93 mg/dl	70-99mg/dl
T. Chol	141mg/dl	<200mg/dl
Bone marrow	72%of plasma cells in the bone marrow with monoclonal paraproteinemia, anemia and renal insufficiency are consistent with symptomatic plasma cell myeloma .	
SPEP	Sharp monoclonal band in Gama region with background immunoparesis, M-26.8g/dl at diagnosis.	
UPEP	negative	
SFLC	K-13, L-838, K/L-0.016	

The definitive diagnosis of cardiac and renal AL amyloidosis secondary to multiple myeloma was confirmed. No other organ involvement by amyloidosis was observed, as indicated by negative findings in GI biopsy, pulmonary imaging, nerve conduction studies, and abdominal ultrasound showing no organomegaly.

A multidisciplinary approach involving a physician, haematologist, cardiologist, and nephrologist was initiated to manage the patient's complex medical condition. Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) therapy was initiated for myeloma and amyloidosis. HFpEF was managed mainly with diuretics furosemide, spironolactone, and empagliflozin. Following good clinical improvement, the patient was discharged, with follow-up appointments scheduled in the respective clinics to monitor disease progression.

The patient's disease process was complicated by an episode of severe right-sided pneumonia, empyema due to underlying immunosuppression, and an acute kidney injury, which warranted Intensive unit care for several days for inotropic support and CRRT. Fortunately, he recovered from that incident.

Eventually, the patient's M band levels decreased significantly to 2.6 g/dl and later became undetectable; urine protein electrophoresis was negative, and the serum-free light chain assay showed a K/L ratio of 1.3. This indicated a complete haematological response to the treatment regimen with CyBorD.

The patient's urine protein-to-creatinine ratio (UPCR) significantly decreased to 1356 mg/g, and the patient's symptoms improved considerably alongside these biochemical and haematological parameters.

Currently, the patient's treatment regimen includes CyBorDe, which entails administering bortezomib at a dose of 2 mg on Days 1, 8, 15, and 22 on a 35-day cycle and dexamethasone 20mg per oral day of and day after each bortezomib. Additionally, the patient is prescribed empagliflozin at 10 mg once daily in the morning, spironolactone at 25mg daily, and oral furosemide at 80 mg twice daily.

Discussion

Amyloidosis is a rare, heterogeneous disorder of protein misfolding due to the extracellular deposition of insoluble, beta-fibrillary fibres in various organs and tissues [1,3]. It is a rare cause of cardiorenal syndrome. It accounts for type 5 cardiorenal syndrome, in which a systemic condition can cause both cardiac and renal involvement [6].

The most common form of systemic amyloidosis, known as light chain amyloidosis (AL amyloidosis), arises from monoclonal plasma cell dyscrasia [8]. AL amyloidosis occurs in 10-15% of Multiple myeloma patients. Cardiac amyloidosis can be caused by AL or ATTR subtypes. ATTR can be either wild-type/ acquired or hereditary [5,7]. ATTR type involves the heart in almost all cases while AL type affects only 50-70 % of the time [8].

Multiple myeloma (MM) is a plasma cell dyscrasia caused by the overproduction of monoclonal immunoglobulins [1,4]. It leads to chronic anaemia, skeletal abnormalities such as Lytic lesions and fractures, spinal cord compression, renal failure, hyperviscosity, peripheral neuropathy, and recurrent infections [9].

Our patient's investigations, including serum and urine protein electrophoresis, revealed monoclonal gammopathy and bone marrow plasma cells comprising 72% of the total, meeting the diagnostic criteria for MM as per the International Myeloma Society [4].

In AL amyloidosis, where the glomerulus is frequently affected, patients often present with significant proteinuria, with more than 65% presenting with nephrotic syndrome [10]. Patients with the AL-lambda subtype typically demonstrate lower serum creatinine concentrations and elevated urinary protein excretion compared to individuals with the AL-kappa subtype [1]. Our patient presented with significant proteinuria.

In cases where AL amyloidosis affects the heart, patients may experience systemic symptoms such as fatigue, malaise complicated by congestive heart failure, arrhythmias, and restrictive cardiomyopathy [11]. Symptoms of heart failure progress rapidly over about a month in cardiac AL amyloidosis. Hypotension occurs as the disease progresses and is contributed by adding ACE inhibitors [1]. Electrocardiographic changes in cardiac amyloidosis include low voltage complexes in the limb leads, poor R wave progression, pathological q waves, and pseudo infarct pattern. Typical findings in 2D echocardiography of amyloidosis include biatrial enlargement, small ventricular cavity, thickening of the interatrial septum, right ventricular free wall thickness, and mild-to-moderate pericardial effusion [1,5].

Diastolic dysfunction and an apical sparing pattern on longitudinal strain imaging are also often observed. However, in late stages, systolic dysfunction can occur. Diffuse subendocardial late gadolinium enhancement with high native T 1 is seen in cardiac MRI [1,5].

Invasive diagnostic criteria for cardiac amyloidosis include demonstrating amyloid fibrils within cardiac tissue or a biopsy from an extracardiac site, accompanied by characteristic cardiac amyloidosis features evident on echocardiography or cardiac magnetic resonance imaging (CMR) [5]. This patient's clinical presentation, electrocardiogram findings, and echocardiography studies showed typical features consistent with cardiac amyloidosis. These, together with the presence of renal AL amyloidosis, confirm the diagnosis of cardiac amyloidosis through invasive criteria, although endomyocardial biopsy was not performed. However, Endomyocardial biopsy is not always essential for diagnosing cardiac amyloidosis [5] if other characteristic findings exist.

Management of AL amyloidosis involves treating the disease process and managing Organ related complications. In managing heart failure, salt and fluid restriction with diuretics play a major role. Caution is needed when using traditional heart failure medications in these patients. Usually, beta blockers and non-dihydropyridine calcium channel blockers are poorly tolerated, and cause pronounced negative inotropic effects due to trapping between amyloid fibrils [1,5]. Angiotensin-converting enzyme inhibitors should be used cautiously, especially in patients with cardiac amyloidosis and autonomic dysfunction [1,5]. There is not enough evidence of benefit of SGLT2 inhibitors in HFpEF in cardiac amyloidosis [12]. Our patient was started on diuretics, fluid, and salt restriction; we have initiated empagliflozin for our patient to manage heart failure and proteinuria.

Chemotherapeutic regimens with CyBorD and autologous stem cell transplantation treat the primary disease condition. Using bortezomib with cyclophosphamide and dexamethasone has shown

hematologic response rates of 62%, renal response rates of 25%, and cardiac response rates of 17%, making bortezumab based therapies the preferred treatment for those not eligible for transplant [13]. Adding daratumumab to the CyBorD regimen was associated with increased frequencies of complete hematological response and survival free from major organ deterioration according to Phase 3 ANDROMEDA trial [15]. Since daratumumab is not available, we have administered CyBorD to him. Studies have suggested that doxycycline could reduce early mortality in patients with cardiac AL amyloidosis [3]. our patient underwent treatment along with doxycycline and is currently on the sixth cycle. After five cycles, our patient had a complete haematological and renal response with therapy. unfortunately, we couldn't assess cardiac response due to the unavailability of BNP testing in the government sector [10]. He is currently under evaluation for a BM transplant with achieved hematological and renal response.

When AL amyloidosis coexists with multiple myeloma, The prognosis is worse [1]. Patients with monoclonal Lambda light chain in urine and nephrotic-range proteinuria experience shorter survival times [3].

Cardiac involvement, particularly congestive heart failure, drastically reduces median survival to less than six months, indicating A dismal prognosis [1,7]. AL cardiac amyloidosis has Worse prognosis than ATTR [11].

Despite poor prognostic factors, our patient has shown biochemicaland clinical improvement with optimal medical treatment.

Conclusions

This case highlights the challenges of managing MM-associated AL amyloidosis, especially when there is cardiac and renal involvement. A comprehensive diagnostic approach, multidisciplinary collaboration, and individualised treatment strategies tailored to the patient's clinical presentation and disease progression are crucial to ensure successful management. Early diagnosis and appropriate treatment of the disease and its complications significantly improve the clinical progress despite overall poor prognosis.

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