Concurrent Challenges: Multiple Myeloma and Cardiac Amyloidosis

Laveena Mehta[1*], Dixant Patel[1], Sandeep Budhiraja[1], Rayaz Ahmed[2]

[1]Department of Internal Medicine, Max Super Speciality Hospital, Saket, New Delhi

[2]Department of Haemato-Oncology, Max Super Speciality Hospital, Saket, New Delhi

Correspondence:

Laveena Mehta

E-mail: laveenamehta33@gmail.com

Abstract: We report a case of 56-year-old male with known case of Hypertension and Hypothyroidism presented with complaints of generalised weakness and weight loss since 8 months (approx. 40kg), tightening in and around the mouth and hoarseness of voice with dysphagia since 6 months, swelling in feet since 3 months, cough and constipation on and off since one month. The laboratory results indicated that the serum calcium (S.Ca2+) level was 14.1 mg/dl and the ionized calcium (Ca2+) level was 1.62 mmol/l. Immunoglobulins were low {IgA- 17 mg/dl (50-410 mg/dl), IgG- 386 mg/dl (650-1500 mg/dl), IgM- 20 mg/dl (60-280 mg/dl); Immunofixation electrophoresis (IFE) revealed positive result for lambda free light chain (Figure 1) and further quantitative value lambda free light chain was high (Lambda free - 2054.89 mg/l). Whole Body FDG PET Scan revealed non-FDG avid lytic lesions at multiple bone sites. In view of suspicion of Multiple Myeloma, bone marrow aspiration and trephine biopsy were done which confirmed the diagnosis of Multiple Myeloma. ECG showed low voltage QRS complexes and 2D echo revealed- Global LVEF 55-60%, Dilated LA, concentric LVH with altered myocardial echotexture, no RWMA, Grade II diastolic dysfunction present (raised LVEDP), RVSP-39mmhg (moderate PAH), findings S/O- cardiac amyloid; which was later confirmed with Cardiac MRI. Abdominal fat pad biopsy revealed area of necrosis but negative for congo red stain (amyloidosis). The patient underwent VCD (bortezomib; cyclophosphamide; dexamethasone) chemotherapy with Daratumumab. By the time of publication, the patient had received autologous stem cell transplantation and after 10 courses of VCD with Daratumumab, repeat bone marrow aspiration and histo-biopsy revealed complete remission of myeloma. The uncommon Multiple Myeloma complication in this clinical case was associated with restricted cardiomyopathy as a result of secondary cardiac amyloidosis. This is true for both Multiple Myeloma and cardiac amyloidosis. When one of these diagnoses is initially established, more investigation should be done to rule out the other illness, keeping in mind the necessity of meeting standard diagnostic criteria and the challenge of conducting an effective diagnostic workup in occasionally complex clinical situations.

Introduction

The hallmark of multiple myeloma (MM) is usually the neoplastic growth of plasma cells that generate monoclonal immunoglobulin. The plasma cells multiply in the bone marrow, causing osteolytic lesions, osteopenia and/or pathologic fractures as well as significant skeletal damage. The cardiovascular system is one of the organs and systems that are implicated in the clinical picture of multiple myopathy. 10-15% of MM patients may experience severe side effects, such as localised or systemic AL amyloidosis, in addition to the underlying disease[2]. There are little worldwide statistics on cardiac amyloidosis and overt multiple myeloma (MM). Nicolaes Fonteyn first reported the disease known as amyloidosis in 1639. It is a collection of clinical disorders brought on by the deposition of soluble immunoglobulin light chains as insoluble fibrils[2,4]. Any organ, including the heart, neurological system, skin and subcutaneous tissue, kidneys and liver, can be impacted by systemic amyloidosis[2,3]. Proteinaceous components resulting from immunoglobulin light chain and transthyretin (TTR), also referred to as prealbumin, can deposit and cause cardiac amyloidosis[5]. Transport thyroid hormone and retinol combine to generate the TT. The National Centre for Health Statistics in the United States reports that there are 4.5 instances of AL amyloidosis for every 100,000 people[5].

The heart (70– 80%), kidneys (74%), liver (27%) and peripheral and autonomic nervous systems (22 and 18%, respectively) are the primary the target organs in AL amyloidosis[6,7] disease. Furthermore, isolated cardiac amyloidosis, an uncommon symptom, is only seen in 5% of individuals[8,9]. Clinical signs of AL cardiac amyloidosis include progressive chronic heart failure (HF) with ascites in the later stages, pleural effusion, peripheral edema in 70% of patients and severe rest dyspnea in 80% of patients[10]. Inhibiting abnormal precursor protein synthesis and plasmocyte proliferation is the main treatment strategy for cardiac amyloidosis in both MM and AL patients. The first-line therapies for MM and systemic AL amyloidosis consist of combining proteasome inhibitors (PIs; bortezomib, carfilzomib, and ixazomib) with other chemotherapeutic medications (cyclophosphamide, melphalan, and dexamethasone) as per guidelines for diagnosis and treatment[9,11]. Proteasome inhibition, however, can also occur in normal cardiomyocytes and/or endothelial cells, in addition to pathogenic plasma cells. This could lead to the development of cardiovascular toxicity. Clinical symptoms can include a decline in systolic function, ischemia development, including myocardial infarction (MI) and other rhythm/ conduction disorders[12,13]. The cardiotoxic effects of glucocorticoids and alkylating medications (cyclophosphamide and melphalan) are comparable[13]. Up to 4% of patients get HF while on bortezomib medication; however, if glucocorticoids are taken concurrently, this incidence can rise to 15%[13,14]. This clinical case report presents a patient diagnosed with multiple myeloma (MM), whose condition was further complicated by severe cardiac AL amyloidosis. It also highlights the intricacy of managing the patient's treatment following the latest cardio-oncology guidelines.

Case presentation

A 56-year-old male with known case of Hypertension and Hypothyroidism presented with complaints of generalized weakness and weight loss since eight months (approx. 40kg), tightening in and around the mouth and hoarseness of voice with dysphagia (only to solids, can tolerate liquid/soft diet) since six months, swelling in feet since three months, cough and constipation on and off since one month. Patient had a family H/O cardiovascular disease. Rest general and systemic examination was normal except for Bilateral pitting pedal edema and macroglossia (USG neck and MRI face and neck revealed: diffuse bulky intrinsic muscle of the tongue). The laboratory results revealed a haemoglobin (HB) level of 12.3 mg/dl, a total leukocyte count (TLC) of 7.6 (10^9/L), and a platelet count (PLT) of 273 (10^9/L), with normal liver and kidney function tests, including urinary calcium. However, the serum calcium (S.Ca2+) was elevated at 14.1 mg/dl, and the ionized calcium (Ca2+) level was 1.62 mmol/l. Immunoglobulin levels were found to be low, with IgA at 17 mg/dl (normal range: 50-410 mg/dl), IgG at 386 mg/dl (normal range: 650-1500 mg/dl), and IgM at 20 mg/dl (normal range: 60-280 mg/dl). Additionally, Beta-2 microglobulin was significantly elevated at 7.784 (normal range: 0.9-2.7). Immunofixation electrophoresis (IFE) revealed positive result for lambda free light chain {FIG 1} and further quantitative of value lambda free light chain was high (Lambda free - 2054.89 mg/l). Whole Body FDG PET Scan revealed multiple non-FDG avid lytic lesions involving bilateral scapulae, body of sternum, bilateral clavicles, bilateral acetabulum, D5, D6, L3 & L5 vertebral bodies, left 12th rib posteriorly, left ala sacrum, bilateral iliac bones and bilateral proximal femur. In view of suspicion of Multiple Myeloma, bone marrow aspiration and trephine biopsy were done which revealed 70% plasma cells and 90% CD138 positive plasma cells of all nucleated cells {hypercellularity (90%)} respectively, features consistent with plasma cell myeloma.

Meanwhile, baseline ECG was obtained which showed low voltage QRS complexes, ectopics with ST depression in antero-lateral leads and T-wave inversion in V3-V6(FIG.3); along with raised cardiac enzymes and 2D echo was done which revealed Global LVEF 55-60%, Dilated LA, concentric LVH with altered myocardial echotexture, no RWMA, Grade II diastolic dysfunction present (raised LVEDP), RVSP-39mmhg (moderate PAH), findings S/O- cardiac amyloid; which was later confirmed with Cardiac MRI (Figure 2).

Laboratory results	11/01/2023	21/01/2023	06/05/2023
S. calcium (mg/dl)	14.1	8.3	8.5
Total Protein (g/dl)	5.6	5.4	4.4
Creatinine (mg/dl)	1.0	0.8	0.6
Ionised Calcium (mmol/l)	1.62	1.35	
Trop-I (ng/ml)	0.17	0.15	
NTproBNP (pg/ml)	6432	4737	2370
eGFR (ml/min/1.73 m^2)	77.19	99.85	139.02

Table 1: Laboratory results of the case presentation

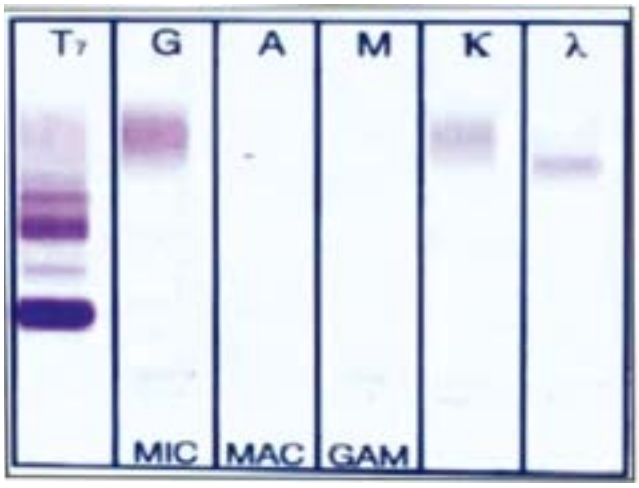

Figure 1: Immunofixation electrophoresis (IFE) revealed positive result for lambda free light chain corresponding to suspicious M spike

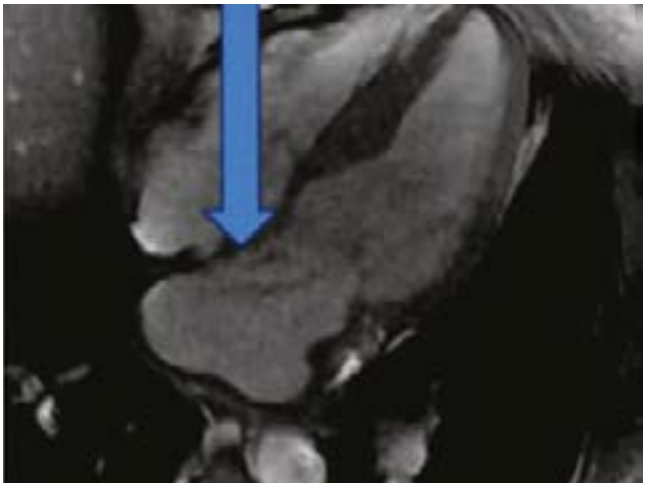

Figure 2(B): Dilated left atrium

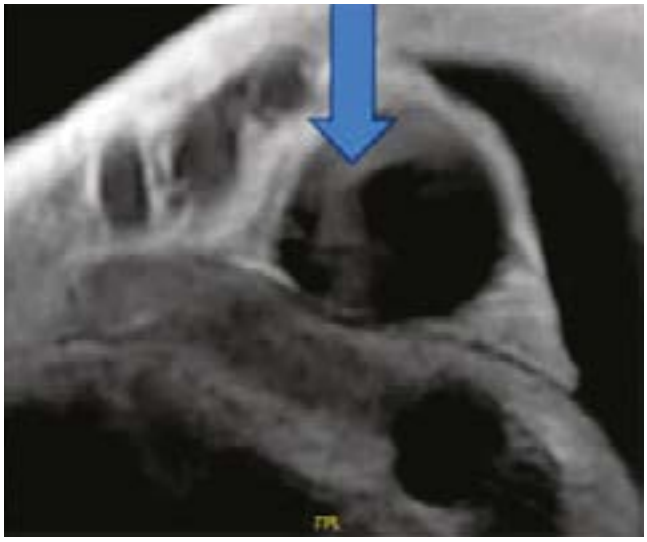

Figure 2(A): Myocardial enhancement suggestive of infiltration and likely amyloidosis

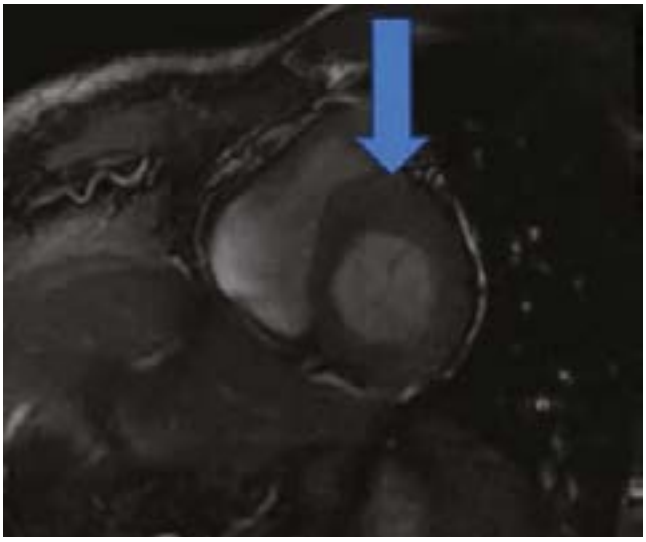

Figure 2(C): Concentric hypertrophy of left ventricle

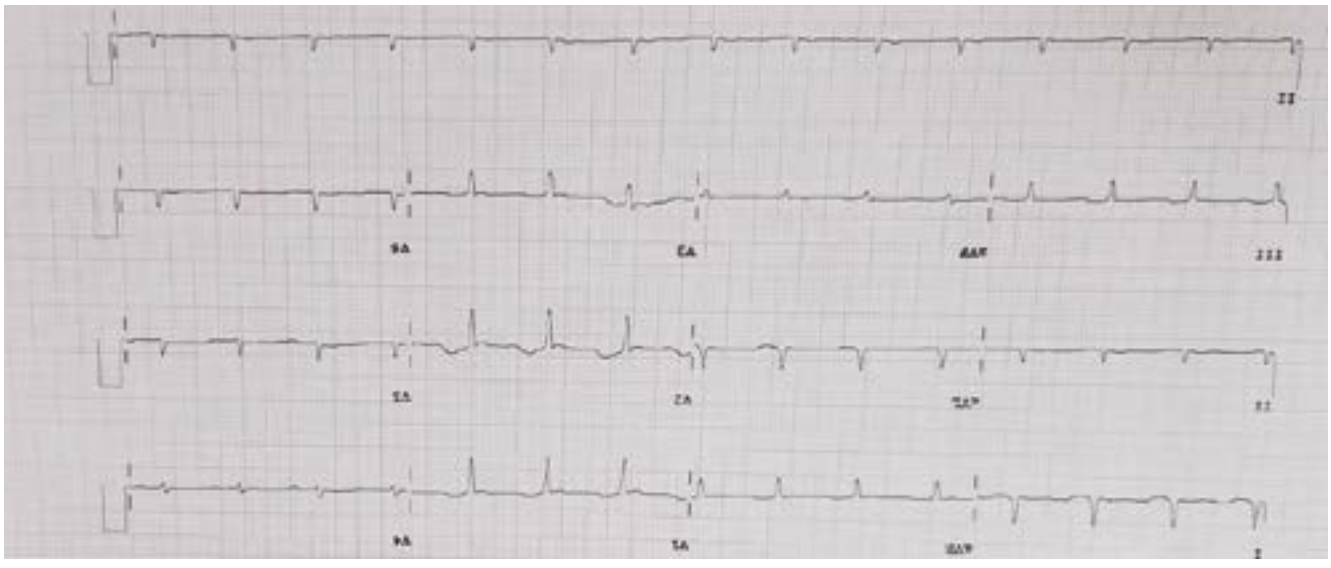

Figure 3: 12 lead ECG showed low voltage complexes, ectopics with ST depression in antero-lateral leads and T-wave inversion in V3-V6

US guided trucut biopsy of abdominal fat pad was done which showed mature fat with areas of fat necrosis. No apple birefringence under polarised light with Congo Red staining (negative for amyloid), but the combination of clinical features (macroglossia, bilateral pedal edema, hoarseness of voice, fatigueness) along with cardiovascular findings (including ECG, 2d-Echo and Cardiac MRI) in the background of Multiple Myeloma was highly suggestive of Cardiac Amyloidosis. The pathological biopsy is the only means to confirm myocardial amyloidosis, but negative results of Congo-red staining do not rule out myocardial amyloidosis[15]. So patient was diagnosed as a case of Multiple Myeloma with Cardiac Amyloidosis.

Treatment

The Patient was started on specific treatment, Inj. Dexamethasone 20mg. Diuretics are the mainstay of supportive care in cardiac amyloidosis. Torsemide [20mg, twice daily] and Spironolactone (50mg, twice daily) were used to alleviate cardiac pre-load and edema. Autologous stem cell transplantation was done after 3 months. After 6 months and 10 courses of Daratumumab with Bortezomib, cyclophosphamide and dexamethasone (VCd), repeat bone marrow aspiration and histo-bone marrow biopsy showed - plasma cells accounted for 3% of the cell count on flow cytometry & CD138 positive plasma cells are 1% of all nucleated cells, respectively; with the patient showing complete remission.

Discussion

Multiple Myeloma and Amyloidosis are two distinct but related entities that use distinct pathogenetic processes to inflict damage and failure in important target organs[15]. Globally, there is variation in their estimated occurrence. In general, the incidence of MM is roughly five times higher than that of AL. For example, in Spain, the estimated crude incidence of Amyloidosis in 2018 was 1.19/100,000 person-years 18, while incidence rate of MM in the last ten years was approximately 5/100,000 person- years. The estimated crude incidence in 2021 was 6.7[16,17]. Insoluble homomeric amyloid fibrils, which are made up of different serum proteins, progressively replace normal tissue in different human organs as a result of the systemic, organ-limited disease amyloidosis[19]. Six subtypes of major heart related amyloidosis can be distinguished in the clinical setting, (1) AL, or primary amyloidosis; (2) AA or secondary amyloidosis; (3) familial (hereditary) am yloidosis; (4) senile systemic amyloidosis, also referred to as wild type transthyretin; (5) isolated atrial amyloidosis; and (6) haemodialysis-related amyloidosis, which is caused by beta-2 microglobulin accumulation20. Out of all patients exhibiting cardiac dysfunction, fewer than 5% have familial syndrome s, 10% have AA amyloidosis and up to 50% have AL amyloidosis21. Patients with AL amyloidosis is diagnosed at an average age of 64 years old[24].

The pericardium, endocardium and conduction system may also be affected by amyloid depositions, which primarily affect the interstitium of the contractile myocardium[25]. A poor prognosis is generally associated with significant morbidity when there is cardiac involvement[26,28]. Early diagnosis and vigorous treatment of plasma cell dyscrasia may change prognosis in cases of cardiac amyloidosis (CA), i.e. with chemotherapy and autologous stem cell transplantation improve clinical outcomes[29,30].

Our patient was a tall, 56-year-old male who arrived complaining of pedal edema, dysphagia and voice hoarseness along with loss in weight. It is crucial to stress that even while systemic light-chain amyloid illness only affects 10% of individuals with multiple myeloma, their prognosis is very bad, particularly if they also have cardiac amyloidosis[22,23]. Patient was evaluated and serum calcium was found to be 14.10, lambda free chain in serum was found to be very high, serum electrophoresis showed no M spike and PET CT showed Non FDG avid osteolytic lesion of bone at multiple sites. Following evaluation, a bone marrow sample was performed, confirming the multiple myeloma diagnosis.

ECG, echocardiography and cardiac MRI are also important proofs for the diagnosis of myocardial amyloidosis. A study describing the clinical characteristics of eight patients with cardiac amyloidosis caused by MM found that seven cases out of eight (87.5%) showed low li mb lead voltage, six (75.0%) cases had poor precordial R-wave progression or pseudo-necrotic Q wave and three (37.5%) cases present with ST-T wave abnormalities[32]. Studies have shown that the most characteristic ECG manifestation in patients with myocardial amyloidosis is the low-voltage pattern[31]. Typical echocardiography is characterised by thickening of the left ventricular wall with a granular sparkling appearance in the absence of hypertension and a limited or diffuse tissue enhancement of the heart by gadolinium on MRI.

A baseline ECG in our patient showed low voltage QRS complexes, ectopics with ST depression in Anterolateral leads and T wave inversion along with high cardiac Biomarkers. Following it, ECHO was done which was suggestive of amyloidosis. To confirm the diagnosis Cardiac MRI with gadolinium contrast was performed which showed presence of myocardial enhancement along with dilated Left Atrium and concentric hypertrophy in left ventricle with normal ejection fraction suggestive of restrictive cardiomyopathy.

Congo Red staining of biopsy tissue can be used to confirm myocardial amyloidosis if results on echocardiography, MRI and ECG are positive. However, negative results from Congo Red staining do not rule out myocardial amyloidosis[15]. Although, blind examination of kidney, abdominal adipose and intestinal tissue are frequently employed in place of myocardial biopsy due to the poor heart function in patients with myocardial amyloidosis. The positivity rates of different tissue specimens stained with Congo Red were reported as follows, abdominal fat, 50–80%; bone marrow, 56%; rectum, 75%; kidney, 94%; carpal ligament, 82%; liver, 97%; small intestine, 83%; skin, 90%; sural nerve, 86% and heart, 100%. However, the buccal mucosa was the most common site of amyloid deposition in the oral cavity, followed by the tongue, palate, gingiva and floor of the mouth.

In this patient Abdominal Fat pad biopsy was done which revealed area of fat necrosis which was negative for Congo red stain and so for amyloid. The patient had indentations on the tongue and suffered from macroglossia. Taking patient's wish into consideration, an invasive biopsy could not be taken.

But keeping the clinical features and imaging in mind, a diagnosis of multiple myeloma with cardiac amyloidosis was made and the patient was started on diuretics, chemotherapy and autologous stem cell transplantation. The Patient responded well to the treatment and repeat bone marrow histo-biopsy and aspiration revealed complete remission of myeloma and a normal MUGA scan post-chemotherapy. Hence proving that early diagnosis and treatment has a great impact on prognosis.

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