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Case Report

Challenges in the Diagnosis of Plasma Cell Neoplasm with Idiopathic Amyloid-Like Deposits: A case Report with the Review of Literature

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ABSTRACT

Light-Chain Plasma Cell Myeloma (LC-PCM) is a more aggressive and a less frequent type of PCM with poorer prognosis. It is characterized by the inability of the malignant plasma cells to produce heavy chains and resulting in the exclusive production of light chains. We present a case of LC-PCM with two diagnostic challenges that were faced during the diagnosis: the first was increased plasma cells (65%) in the bone marrow without any CRAB features (hypercalcemia, renal failure, anemia, and lytic bone lesions) primarily presenting as cardiac failure which is an uncommon finding. The second challenge was serum protein electrophoresis with immune fixation revealed no heavy chains along with a serum-free light chain ratio of 0.011. Myeloma defining events described in recent WHO classification along with biomarkers for diagnosing PCM helped us in arriving at the diagnosis of LC-PCM. Another diagnostic issue was the presence of prominent interstitial and vessel wall deposition of eosinophilic and extracellular amorphous material. This material was negative for periodic acid-Schiff stain and Congo red and did not show any apple green birefringence on polarization microscopy, black in silver, and blue in trichrome stains suggesting the presence of idiopathic amyloid-like deposits.

Keywords: Light-chain plasma cell myeloma; Amyloid-like deposits; Serum free light chain assay; Plasma cell myeloma; Monoclonal immunoglobulin deposition disease

INTRODUCTION

Plasma cell neoplasms are the broad category of hematological malignancy characterized by abnormal proliferation of plasma cells and uncontrolled production of monoclonal immunoglobulins and or increased production of Serum Free Light Chains (SFLC) [1]. It is a spectrum of disorders ranging from a pre-malignant condition such as monoclonal gammopathy of underdetermined significance to a paraneoplastic syndrome such as polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS syndrome) on either end of the spectrum [1,2]. Among these disorders, Plasma Cell Myeloma (PCM) is commonly encountered in hematological practice and accounts for 10% of all hematological malignancies and 1% of all malignancies [1-3]. In 2017 WHO updated criteria for diagnosing PCM included myeloma defining events which included end-organ damage defining hypercalcemia, renal failure, anemia and lytic bone lesions (CRAB features) along with the biomarkers of malignancy (≥ 60% clonal bone marrow plasma cells, involved to uninvolved serum free light chain ratio ≥ 100 or >1 focal lesion on magnetic resonance imaging (MRI) studies of ≥ 5 mm in size) [1,4]. The median age of presentation is 65 years [4,5]. The most common type of monoclonal (M) protein found in PCM is immunoglobulin IgG followed by IgA and IgM [6,7]. Light-Chain Plasma Cell Myeloma (LC-PCM) is a more aggressive and a less frequent type of PCM with poorer prognosis. It is characterized by the exclusive production of light chains due to the inability of the malignant plasma cells to produce heavy chains [8,9].

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Plasma cell myeloma can cause immunoglobulin light chain amyloidosis or can be associated with Monoclonal Immunoglobulin Deposition Diseases (MIDD) [1-3].

Amyloids are abnormal protein aggregates that are amorphous eosinophilic hyaline extracellular deposits characterized by apple-green birefringence by polarizing microscopy, cross beta-pleated sheet structure with a non-branching fibrillary morphology of 7-10 nm in diameter. It is caused by the deposition of light chains of immunoglobulins or their fragments. It may present either as primary amyloidosis in PCM cases or as secondary amyloidosis in association with chronic inflammatory conditions [10]. However, in clinical practice, it is not uncommon to come across certain extracellular deposits or materials which are commonly confused as amyloid and are called amyloid-like deposits [10,11]. We present here one such case which is less frequently encountered in PCM along with associated clinical condition which poses challenges in arriving at the final diagnosis.

CASE PRESENTATION

A 55-year-old male patient presented to the hospital with the chief complaints of progressively worsening exertional breathlessness for four months and bilateral swelling of lower limbs for the one-month duration. He was recently found to have retroviral positive status and type II diabetes mellitus. There was no history of chest pain, fever, bleeding manifestations, bone pain, or oliguria. The patient was a non-smoker, non-alcoholic, and had no history of coronary artery disease in the past.

On examination, the patient was moderately built and nourished with extensive tinea over the entire body and anasarca. His heart rate was 92/minute with a blood pressure of 114/70 mm Hg and elevated jugular venous pressure of 15 cm of water with prominent apical S4 suspecting the presence of cardiac failure. There was mild pallor and no evidence of icterus, cyanosis, clubbing, or generalized lymphadenopathy.

Because of suspected cardiac failure, an electrocardiogram and echocardiogram (Figure 1) were performed which showed sinus rhythm, low voltage complexes in limb leads, and QS complexes in the anteroseptal and inferior leads. An echocardiogram showed significant concentric left and right ventricular hypertrophy, thickened interatrial septum, left ventricular ejection fraction of 21%, grade III diastolic dysfunction grade, moderate tricuspid regurgitation, hepatic flow reversal in inspiration and mild pericardial effusion. The interventricular septum had a granular sparkling appearance with a systolic diameter of 15 mm. Global longitudinal strain by speckle tracking showed a cherry on the top pattern which is classical for cardiac amyloidosis. His right heart catheterization revealed elevated mean right atrial pressure of 16 mm Hg, right ventricular end-diastolic pressure of 24 mm Hg, left ventricular end-diastolic pressure of 30 mm Hg, and mean pulmonary artery pressure of 27 mm Hg. Cardiac MRI with contrast enhancement revealed hypertrophy of the left ventricle with global hypokinesia, global transmural late gadolinium enhancement mainly involving the septum and the lateral wall, and great vessels were unremarkable. Mild pericardial and mild bilateral pleural effusion was noted. A clinical working diagnosis of congestive cardiac failure with biventricular dysfunction, restrictive cardiomyopathy, and likely etiology of cardiac amyloidosis was made. Both systolic and diastolic dysfunction was seen in our case probably due to the progression of restrictive cardiomyopathy to severe left ventricular dysfunction. Given the possibility of cardiac amyloidosis, an abdominal fat pad biopsy was sent for histopathological examination; however, no amyloid deposits were seen.

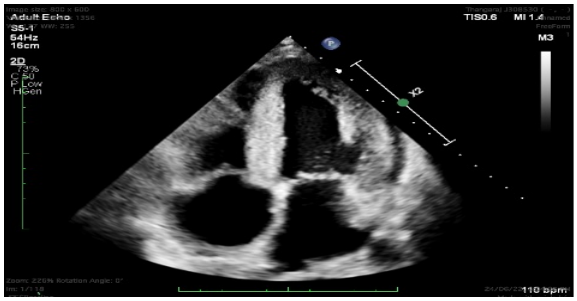

Figure 1: Apical four chamber view of 2D echocardiogram showing biventricular hypertrophy, thickened interatrial septum, sparkling interventricular septum and mild pericardial effusion.

Simultaneously patient was worked up for plasma cell neoplasm. His baseline hemogram revealed hemoglobin of 116 g/L, total white cell count, and platelet count of 14.3 × 10^6 cells/ L and 170 × 10^9/ L respectively with an erythrocyte sedimentation rate of 20 mm at the end of one hour. Peripheral smear examination revealed normocytic normochromic red cells with no rouleaux formation, mild leukocytosis, and normal platelet count. No circulating plasma cells were noted and the patient did not have any CRAB features (serum calcium: 9.1 mg/dL, serum creatinine: 1.3 mg/dL, hemoglobin: 116 g/L, and no bone lytic lesions). Serum protein showed normal total protein (5.5 g/L) with reversal of albumin to globulin ratio and electrophoresis showed hypoalbuminemia (2.4 g/L) but no M band was noted. Serum protein immune fixation showed only lambda band, no IgG, IgA, IgM, or kappa band was detected. The determination of serum free light chains found a high level of lambda at 1870 mg/L, kappa at 20 mg/L, and serum free light chain ratio was 0.011. Beta-2 microglobulin was elevated (6631 ng/ ml), and 24-hr urinary protein showed nephrotic range proteinuria (5 g/day), however, urine Bence-Jones protein was not detected. His HbA1c was 6.8% and liver enzymes were normal.

Bone marrow aspirate and imprint smear showed increased plasma cells (65%) having predominantly mature forms and few immature forms along with suppressed trilineage hematopoiesis. The corresponding trephine marrow biopsy showed diffuse infiltration by plasma cells and was highlighted by CD38 and CD138 Immunohistochemical (IHC) stains, kappa and lambda IHC stains were non-contributory along with the prominence of interstitial and vessel wall deposition of eosinophilic and extracellular amorphous material. This material was negative for Periodic Acid-Schiff (PAS) stain and Congo red stain. No apple green birefringence detected on polarization microscopy (Figure 2), black in silver, and blue in trichrome stains. Overall diagnosis of plasma cell myeloma was given and advised for further serum protein immune fixation including IgD, IgE and

all subsets of immunoglobulins were negative, thus the final diagnosis of LC-PCM with idiopathic amyloid-like deposits was made. The patient was started on diuretics, antifungals for tinea, antiretroviral therapy, and chemotherapy for multiple myeloma. However, patient succumbed a few days later to pneumonia and septic shock.

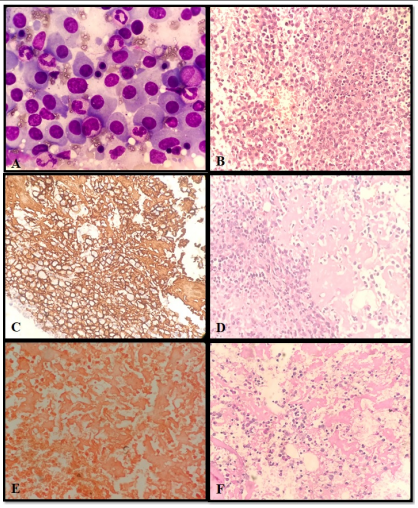

Figure 2: Bone marrow aspirate and imprint smear showed increased plasma cells. **Note:** (A) Bone marrow aspiration shows increased plasma cells with suppressed trilineage hematopoiesis (Giemsa stain, 1000x); (B) Bone marrow trephine biopsy shows diffuse infiltration by plasma cells (H & E stain, 400x); (C) Plasma cells are positive for CD138 immunohistochemistry (400x); (D) Amorphous extracellular amyloid-like deposits; (H & E stain, 400x) which are negative for Congo red stain (400x) (E) and periodic acid Schiff stain (400x) (F).

DISCUSSION

In the present case report, two diagnostic difficulties were faced which included a diagnosis of PCM in the absence of CRAB features and the presence of amyloid-like deposits in the bone marrow. Firstly, the diagnosis of PCM was addressed by the biomarkers of malignancy (≥ 60% clonal bone marrow plasma cells, involved to uninvolved serum free light chain ratio ≥ 100 or >1 focal lesion on MRI studies of ≥ 5 mm in size) [1-3,8]. In 2017 WHO updated criteria for diagnosing PCM included myeloma defining events which included end-organ damage defining CRAB features along with the above biomarkers. These biomarkers were not included in the 2008 WHO criteria for diagnosing PCM [1]. In the present case, there was the fulfillment of two biomarkers i.e., the presence of 65% of plasma cells in the bone marrow and the involved/uninvolved SFLC ratio was ≥ 100. Initial serum immunofixation revealed only lambda band without any immunoglobulin band (IgG, IgA, IgM) and subsequently, the remaining subsets of immunoglobulins (IgE and IgD) were negative, thereby confirming the diagnosis of LC-PCM.

LC-PCM constitutes approximately 15% of patients with PCM [6,9]. These patients are frequently associated with bone disease, renal failure, and systemic light chain AL amyloidosis. LC-PCM when compared to IgG or IgA variant of PCM has an earlier average age of onset and appears to have a poorer prognosis [6-9,10]. In our case, the major presenting feature was a cardiac failure with amyloid-like deposits. Plasma cells in LC-PCM at the DNA level show rearrangements in immunoglobulin heavy chains (IgH) thereby resulting in an inability to produce IgH. One IgH allele in most conditions has a germline configuration, whereas the second allele is involved in translocation. It is in contrast with classical PCM where one allele has a functional rearrangement and the second allele is usually involved in a translocation [12-16].

The second diagnostic issue was the presence of eosinophilic and extracellular amorphous deposits in the bone marrow. Special stains can be utilized to differentiate these amyloid-like deposits as illustrated in Table 1. Others material like fibrin, collagen, necrosis, mucin, and gelatinous transformation which are not exactly deposits, has to be first ruled out by using special stains along with clinical condition [10]. The various differential diagnosis for amyloid-like deposits in bone marrow includes Light Chain Or Heavy Chain Deposition Disease (LCDD/ HCDD), or both which are now described under MIDD [1-3]. They differ from amyloidosis as these deposits lack affinity for Congo red and do not have a fibrillar structure [10]. MIDD shows the involvement of various organs including the kidney, skin, heart, liver, lungs, bone marrow, and gastrointestinal tract [11]. Similar to cardiac amyloidosis, echocardiography may reveal diastolic dysfunction and a reduction in myocardial compliance in MIDD [12,15,16].

Table 1: Special stains to differentiate amyloid-like deposits.

Lesions	Congo red	PAS stain	Silver stain	Masson trichrome stain
Amyloid	Positive	Negative	Negative	Blue
Light chain/ heavy chain disease	Negative	Positive	Negative	Blue
Collagen	Negative	Negative	Negative	Blue
Diabetic mellitus	Negative	Positive	Black	Blue
Idiopathic	Negative	Negative	Black	Blue

Light chain/heavy chain deposits can be PAS stain positive and, in our case, the extracellular deposits were negative for PAS stain. Light chain deposits are better appreciated on immunofluorescence when compared with IHC. Even in diabetes, PAS-positive deposits can be seen in the blood vessels [10]. The exact nature of these extracellular deposits was not identified in the present case; hence a diagnosis of idiopathic amyloid-like deposits was rendered.

CONCLUSION

To conclude, correlation with a complete panel of immunofixation and SFLC assay is important for making a diagnosis of LC-PCM with cardiac dysfunction even in the absence of CRAB features. It is not uncommon to see extracellular material which is most often confused with amyloid deposits. Careful attention to clinical features and assessment of other organ dysfunction attributable to the underlying disease

and bone marrow morphology along with special stains is essential for making the correct diagnosis.

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