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Case Report

IGM AL AMYLOIDOSIS WITH UNDERLYING CXCR4 MUTATION PRESENTING AS BRACHIAL PLEXOPATHY: CASE REPORT

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Abstract:
Amyloidosis is a rare systemic disease of protein misfolding. The most common type of amyloidosis is light chain (AL) amyloidosis, in which the amyloidogenic precursor protein is a monoclonal immunoglobulin (Ig) light chain. Very few patients with AL amyloidosis have underlying IgM paraproteinemia. Neuropathy is a common manifestation of AL amyloidosis but is rarely seen as presenting manifestation. Association of amyloidosis with brachial plexopathy has been reported very rarely. Due to its rarity, IgM AL amyloidosis remains poorly studied. Herein, we report a very rare case of IgM related amyloidosis (AL) presenting as brachial plexopathy in 63-year-old male presented with chief complaint of severe fatigue, decreased appetite and significant weight loss and progressive right side upper limb weakness for last one year. Special staining with Congo Red Stain and immunohistochemical staining were further carried out and the diagnosis of systemic amyloidosis was made. Thorough Laboratory tests including protein electrophoresis, molecular test like CXCR-4 Mutation Analysis, MYD 88 (L265P) Mutation assay, Multiple Myeloma FISH Panel were performed to confirm the above diagnosis**.**

Key words: IgM Al amyloidosis; brachial plexopathy; CXCR-4 Mutation

1. INTRODUCTION:

Amyloidosis is a rare systemic disease of protein misfolding which results from extracellular deposition of beta-pleated aggregates of fibrillar pro-teinaceous materials. The most common type of amyloidosis is light chain (AL) amyloidosis, in which the amyloidogenic precursor protein is a monoclonal immunoglobulin (Ig) light chain. It has been suggested that IgM AL amyloidosis should be categorised as a distinct clinical entity with numerous clinical features that distinguish it from non-IgM AL amyloidosis. Due to its rarity, IgM AL amyloidosis remains poorly studied. Light chain amyloidosis secondary to MGUS or Waldenstroms macroglobulinemia carries poor prognosis when cardiac, renal, liver involvement and/or neuropathy are present depending on their severity (1). Neuropathy is a common manifestation of AL amyloidosis but is rarely seen as presenting manifestation (2). Very few patients with AL amyloidosis have underlying IgM paraproteinemia(3).

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Herein, we report a very rare case of IgM related amyloidosis (AL) presenting as brachial plexopathy, long time before other disease related manifestations appeared, and after initiation of treatment, disease behaved refractory to chemotherapy and had fulminant course.

CASE HISTORY

A 63-year-old male presented with chief complaint of severe fatigue, decreased appetite and significant weight loss from two months with no history of fever, night sweats, bleeding from any site, or blood transfusion. He also had history of progressive right side upper limb weakness for last one year. Weakness was more proximal than distal, associated with wasting of right arm. There were no complains of paraesthesia or any other symptoms suggestive of autonomic dysfunction. The patient is hypertensive and diabetic from last 2 years, and under control with oral medications for the same. As there was gradual progression of symptoms but did not cause any limitation to his daily routine and thus, was advised physiotherapy alone.

On clinical examination, had characteristic atrophy of right arm and shoulder associated with motor weakness in all movements of shoulder and elbow joint, mild decrease in sensory perception and diminished deep tendon reflexes for biceps, triceps, and supinator. Left upper limb and lower limb examination was within normal limits.

Laboratory tests including complete blood count and renal function tests were normal. Liver function tests were slightly altered. Total bilirubin was 2 mg/dl, conjugated bilirubin was 0.9 mg/dl, SGOT was 146 U/L, SGPT was 123 U/L and ALP was 796 U/L. Protein electrophoresis revealed monoclonal band in IgM kappa region (0.27 g/dl) and kappa/lambda ratio of 6.0. CECT neck, chest and abdomen revealed multiple cervical, mediastinal, and abdominal lymphadenopathies (maximum size 2*2.5 cm).

Bone marrow examination revealed increased plasma cells (23%), kappa restricted with background amyloidosis.

Cervical lymph node biopsy and its histopathology showed amyloid lymphadenopathy without atypical lymphoid population. Special staining with Congo Red Stain (figure 3 and 4) and immunohistochemical staining were further carried out and the diagnosis of systemic amyloidosis with any of the following possible underlying etiologies were thought.

In order to confirm our diagnosis, following molecular tests were done in which the genomic DNA was isolated from the EDTA-blood sample. The purity of isolated genomic DNA was checked by using ratio of Abs260mm/Abs 280mm as well as in agarose gel and then it was analysed for mutation status.

1. CXCR-4 Mutation Analysis: Mutated (heterozygous)
2. MYD 88 (L265P) Mutation assay: wild type
3. Multiple Myeloma FISH Panel: was negative for translocations 11:14, 4:14, 16:14 and Deletions 13q14, 17p

- NCS and EMG revealed Right Brachial Plexopathy, Axonal Type with C5-C7 Nerve Root Involvement.
- MRI Brain revealed Few Chronic Ischemic Changes.
- 2D Echo revealed normal LV Systolic Function, Grade 1 Diastolic Dysfunction with Mild Concentric LVH.
- Upper GI Endoscopy revealed Severe Gastritis of Fundus and Body.
- MRI Brachial Plexus was normal, suggesting no infiltration or any external compression.
- DCT and ICT were NEGATIVE

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- Cytogenetics revealed 46 XY
- 24 Hour Urinary Protein was 447 Mg/24 Hours.
- NT PRO BNP was 1100 PG/ML.

Based on all these investigations presence of systemic amyloidosis and brachial plexopathy (axonal type), we concluded brachial plexopathy as a manifestation of systemic amyloidosis. Hence our final diagnosis was IgM AL Amyloidosis with underlying CXCR4 Mutation Presenting as Brachial Plexopathy.

Treatment/ Management: –

After confirming the diagnosis, patient was started with Rituximab-bendamustine chemotherapy protocol, and after 1st cycle patient had clinical improvement for constitutional symptoms, gastritis, and reduction in size of lymph nodes although right upper limb neuropathy did not improve. 3-4 days before 2nd cycle patient complained of palpitations and abdominal distension. USG whole abdomen showed gross ascites with coarse liver echotexture (rapid development of chronic liver disease), biochemically revealing deterioration of LFT and very high alkaline phosphatase pointing towards disease progression and infiltration causing obstructive hepatopathy. 2D echo also showed severe grade 3 diastolic dysfunction with intermittent ventricular arrhythmias. Repeat NCS was performed, and it showed asymmetric axonal poly neuropathy involving both lower and upper limbs suggestive of progression.

Considering the above circumstances, patient was continued with the same chemotherapy protocol with dose adjustments as adding third drug could do more harm than benefit in view of underlying comorbidities. After initial transient benefit post 2nd cycle, patient had reappearance of cervical lymph nodes and ascites. Patient was continued with 3rd cycle R-benda dose adjusted with addition of bortezomib and steroids. Post 2 doses of weekly bortezomib and dexamethasone patient developed bilateral pneumonia and sepsis, managed intensively with antibiotics and supportive care, intubated and kept on mechanical ventilator, gradually deteriorated and succumbed to illness.

2. DISCUSSION

IgM associated light chain amyloidosis (AL) accounts for 5–7% of all patients with systemic AL amyloidosis. Amongst patients with Waldenström's Macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL), amyloidosis has been reported in 7.5% of patients, with half of the patients having a coexisting diagnosis of both WM/AL. Patients with IgM AL have more soft tissue, lung and peripheral nerve involvement, whereas cardiac involvement is less common as compared to non-IgM AL patients.(4,5)

Peripheral neuropathy is reported in around 20% cases of AL amyloidosis (2) and its incidence at the time of presentation is much lesser i.e. around 3% with IgM related AL amyloidosis (6–8). Association of amyloidosis with brachial plexopathy has been reported very rarely.(9) In our present case the appearance of neuropathy was almost 10 months before the onset of other symptoms and signs. Peripheral neuropathy associated with IgM MGUS / Waldenstrom's macroglobulinemia can have multiple etiologies like antibody mediated, infiltration by tumor, compression by tumor, amyloidosis, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M protein and Skin changes) and cryoglobulinemia. Hence, nerve conduction study becomes a very important tool in order to differentiate them into two major categories, of which the most common i.e. Anti-myelin-associated glycoprotein

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(MAG) IgM antibodies associated neuropathy is demyelinating type accounting for almost half of the patients (10).

It has been described that Waldenstroms macroglobulinemia at diagnosis can have only plasma cells in bone marrow or may not have any clonal lymphoid infiltrate (1) leading to under diagnosis. This could be resolved only with genetic tests like in our present case; we got cxcr4 mutation positivity with a PCR based assay. Thus molecular tests are important in diagnosing difficult cases at its early stage.

There are two main subtypes of IgM amyloidosis, LPL lymphoplasmacytic lymphoma) type and PPCN (pure plasma cell neoplasm) type with distinct genetic and morphologic features have been identified. Patients in the PPCN group exhibit genetic changes comparable to those with non-IgM amyloidosis, with prevalence of t(11;14) being 60% vs. 50%, respectively, and none of these patients have MYD88 or CXCR4 mutations. MYD88 mutation was seen in the majority of patients with LPL morphology and CXCR4 mutation is seen in a third of such patients, which is similar to observations in WM.(4,5)

Because of rapid fulminant course of this disease, the patient became symptomatic for the disease causing multi organ failure including hepatic and cardiac failure which emphasises early diagnosis and treatment initiation in a case of systemic amyloidosis in order to avoid complications. Thus any form of neuropathy, especially in elderly should be evaluated well with bone marrow examination and serum protein electrophoresis to pick up these cases early, as early intervention is the best way to improve prognosis. Moreover, refractory nature of disease in spite of baseline normal renal function, mildly deranged cardiac function and low light chain ratio which are considered as strongest prognostic factors in case of amyloidosis. Several risk models have been proposed over time (11) emphasising the importance of neuropathy and liver involvement too (1,4) which needs further verification.

Treatment of AL amyloidosis should be risk-adapted and response-tailored. Rapidly-acting induction regimens followed by high dose therapy and autologous stem cell transplantation in first remission is the treatment of choice in suitable patients.(10) Underlying disease morphology and genetic changes should be carefully reviewed at diagnosis and treatment should be focused on the underlying clonal disease. Patients with AL amyloidosis require a deep response to eliminate amyloidogenic light chains, which is the best predictor of organ improvement. For patients with PPCN morphology, treatment approaches similar to non-IgM AL amyloidosis can be undertaken and for LPL morphology patients, treatment should include a combination of rituximab, an alkylating agent, and bortezomib to target both the lymphoid and plasmacytic components of the disease.(5, 11)

3. CONCLUSION:

Hereby we conclude that for better prognosis of patients with IgM and WM associated peripheral neuropathies, early recognition of the problem, accurate diagnoses using molecular studies and timely therapeutic intervention with effective and non-neurotoxic therapies targeting the underlying clonal mutation are must. There is need for more Clinical trials in order to evaluate the efficacy of emerging therapies and to incorporate them in actual clinical practice.

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BIOPSY IMAGES

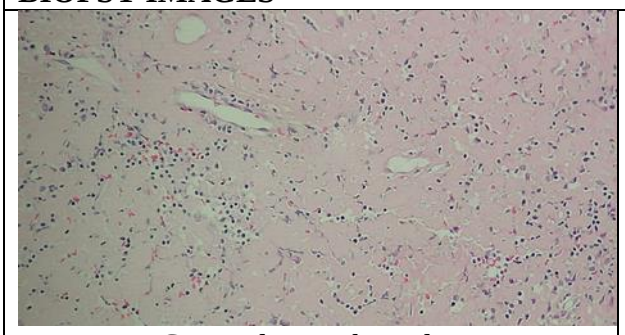

Fig. 1: Cervical Lymph Node Biopsy.

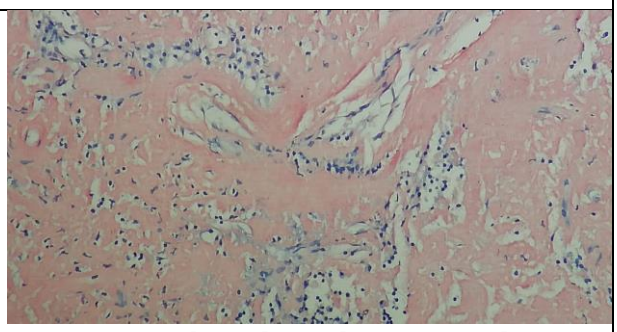

Fig. 2: Lymph Node With Congo Red Stain Highlighting Amyloid Deposits.

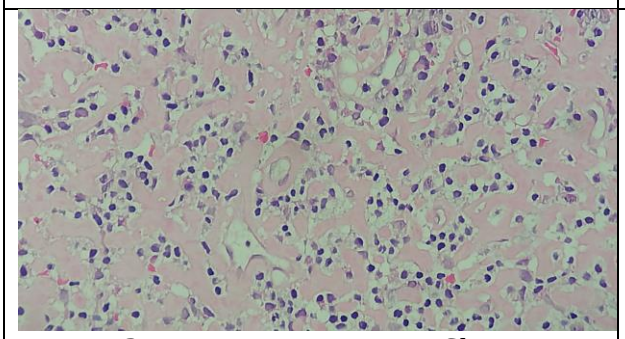

Fig. 3: Bone Marrow Biopsy Showing Diffuse Infiltration Of Plasma Cells With Aggregates.

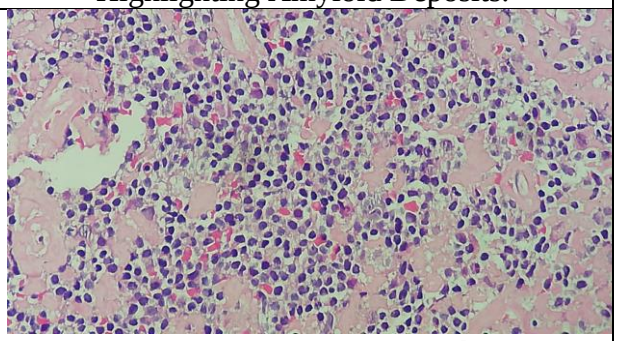

Fig. 4: Bone Marrow Biopsy With Congo Red Stain Highlighting Amyloid Deposits.

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