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POLYNEUROPATHY ASSOCIATED WITH IGA PARAPROTEINEMIA: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Paraproteinemia is precipitated by an accumulation of monoclonal plasma cells or B lymphocytes. Idiopathic neuropathies that are associated with paraproteinemia account for only 10% of the neuropathies. Paraprotein acts like an antibody and is targeted against myelin and axons present in the peripheral nerves. Despite being of interest for quite a long time, the causal relationship between paraproteinemias and peripheral neuropathies still remains a sorcery. We report a case of a middle aged male who presented with pain and paresthesias in both arms and legs. His workup revealed him to be having a paraproteinemic neuropathy consistent with IgA Lambda chains that account for being the most rare type of monoclonal gammopathy than IgM or IgG having the potential to progress to smouldering multiple myeloma.

KEY WORDS: Monoclonal gammopathy; Paraproteinemia; Peripheral neuropathy; Multiple myeloma

INTRODUCTION: Paraproteinemic neuropathies are a heterogeneous group of neuropathies, which share the common feature of a homogeneous immunoglobulin in the serum. Approximately 10% of all idiopathic neuropathies are associated with paraproteinemia.^[1] Monoclonal gammopathy of undetermined significance (MGUS) occurs in over 5.3% of the general population over the age of 70 and the incidence increases with age being more common in men.^[2] The type of M protein in monoclonal gammopathy associated with peripheral neuropathy is most commonly IgM while IgG and IgA neuropathies are less common.^[3] In one study, approximately 60% of neuropathies associated with monoclonal gammopathy were IgM, 30% were IgG, and 10% were IgA. ^[4] IgA protein appears to be associated with a lesser predilection for causing peripheral neuropathy compared to IgM or IgG MGUS combined.^[5] In a study of 74 patients with MGUS, 8 of 26 IgM MGUS patients (31%) had neuropathy, compared to 2 of 34 IgG MGUS patients (6%) and 2 of 14 IgA MGUS patients (14%).^[5] Paraproteinemic

neuropathy IgA affects some or all sensory modalities which cause allodynia, hyperpathia, cramps with distal weakness. These neuropathies are typically manifested neurologically as a demyelinating type of sensori-motor polyneuropathy. Sometimes, multi-organ involvement is also seen. Patients with paraproteinemic neuropathy have an increased risk of axial bone fractures, thrombo embolism, peripheral neuropathy and secondary malignancies.^[6] Therapies for IgA paraproteinemic neuropathy depend on the particular subtype, the patho-physiology involved, ranging from intravenous immunoglobulins (IVIGs), plasma exchange sessions, corticosteroids, rituximab and various chemotherapies. In terms of response to therapy there is no distinction seen between demyelinating and axonal patterns of neuropathy, Possible malignant conversion of underlying benign monoclonal gammopathy has to be closely monitored with risk factors for malignant transformation including progressive worsening of neuropathy and rising titers of monoclonal protein.^[7]

Case Report:

A 52 years of age Pakistani male presented to neurology clinic with a 12 months history of numbness, tingling, pain in both lower extremities and symptoms progressed to involve both his arms for 6 months. Three months prior to presentation he started developing slowly progressive asymmetrical weakness of both legs, without any sphincteric involvement. There was no history of fever, cough, diarrhea or constipation. There was no past history of joint pains, weight loss, photosensitivity, polyuria or polydipsia. He belongs to a poor socioeconomic group and is a gardener by occupation with 3 children. He is a nonsmoker and denies alcoholism. There is history of essential hypertension for 3 years and he is on tablet atenolol 50mg daily. Rest of the drug and family history were nil of note. On physical examination, a middle-aged gentleman alert and oriented to time, place and person. The patient's oral temperature was 98.6°F with a regular pulse of 68 beats/minute. His blood pressure was 130/80 mm Hg with no postural drop and respiratory rate was 14/ minute. He had distal wasting of lower extremities with bilateral footdrop (Figure, A). Muscle tone was decreased in all four limbs with areflexia and bilaterally mute plantar response. He had a Medical Research Council (MRC) sum score of 30/60. Pin prick sensation was lost in a glove and stocking distribution with normal perianal sensation. He had a high steppage gait. Signs of meningeal irritation were absent. Abdominal examination was did not reveal any palpable mass, organomegaly or ascites. The patient's precordial examination revealed normal heart sounds and chest examination revealed normal vesicular breathing. The laboratory analysis demonstrated a normal blood complete picutre and erythrocyte sedimentation rate. Liver and renal function tests, serum glucose levels, muscle enzymes, ECG and chest X-ray were unremarkable. His nerve conduction studies and electromyography were consistent with a chronic sensori-motor demyelinating type of polyneuropathy with secondary axonal damage (Figure, B). Lumbar puncture for CSF analysis showed elevated CSF protein of 0.92g/l. His HbA1c, thyroid function tests, and serum B12 levels were normal. His ANA, RA factor, HIV serology, HbsAg, and anti-HCV were negative. CT scan of the chest, abdomen, and pelvis were unremarkable. Serum protein electrophoresis revealed a discrete spike in the monoclonal paraprotein consisting of IgA Lambda with serum IgA levels markedly raised to 13 mg/dl (Normal range 1-7 mg/dL) (Figure, C) Urine for Bence Jones proteins didn't show light chains. Bone scan, skeletal survey and bone marrow biopsy were negative. Our patient fulfilled the

criteria for MGUS established by the International Myeloma Working Group and the World Health organization consistent with IgA lambda monoclonal gammopathy, Therefore, the final diagnosis of IgA paraproteinemic neuropathy associated with MGUS was made. The patient was given a trial of 5 sessions of plasmapheresis. Mild improvement in motor and sensory symptoms was observed, however, his bilateral foot drop persisted. He was given an ankle-foot-orthosis (AFO) for his foot drop. He is undergoing physiotherapy and has been advised regular follow ups in Neurology and Oncology clinics to plan for immunomodulatory treatment.



Figure A: BILATERAL FOOT DROP

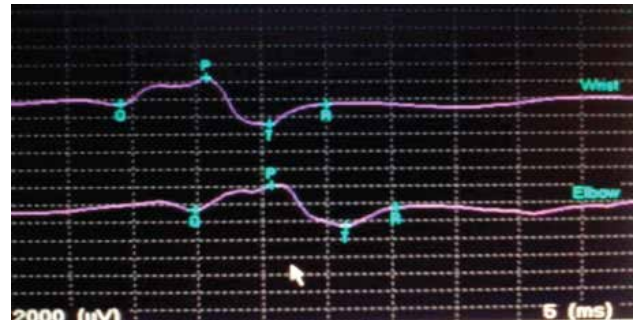


Figure B: Figure B: Nerve Conduction studies showing a demyelinating pattern with a motor amplitude drop, prolong latencies and an abnormal temporal dispersion

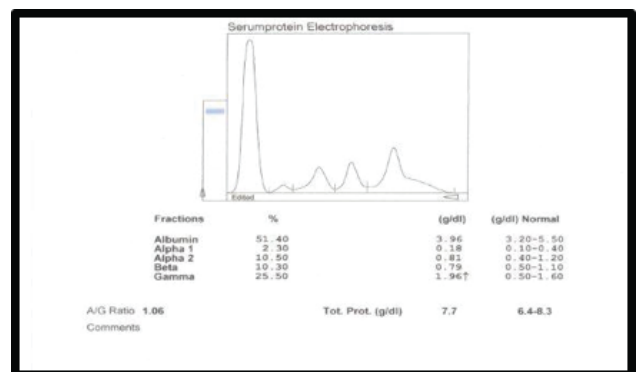


Figure C: Serum protein electrophoresis showing an IgA spike (arrow head)

DISCUSSION:

Patients with paraproteinemic disorders exhibit distinct neuropathic phenotypes, often with characteristic identifiable clinical features. Frequently prognosis is not well-defined and in many cases is still unknown. Neuropathies can lead to disability, loss of independence and social isolation especially in the elderly. They warrant adequate work up for diagnosis which may sometimes be very extensive. Neuropathies associated with paraproteinemia have heterogeneous clinical, neurophysiological, neuropathological and hematological features. These necessitate prompt and appropriate work up and management to avoid permanent disability. There is no known role until now for chemotherapy and no treatment is recommended and required for patients with MGUS.^[8] These patients must be followed over time with history and clinical assessment for disease progression. All patients should undergo laboratory evaluation for disease progression six months after diagnosis with serum and urinary M-protein, complete blood count, creatinine, and serum calcium. Periodic laboratory testing should then be done in follow-up of high-risk patients using a risk stratification system as not all persons with MGUS have the same risk of disease progression. Therefore, the management of a patient with MGUS requires an understanding of the risk of progression to symptomatic disease requiring therapy. MGUS neuropathy is closely linked to chronic inflammatory demyelinating polyneuropathy.^[9] However, this association still remains unclear. The paramount feature of CIDP i.e conduction blocks sometimes occur in MGUS as well. The cerebrospinal fluid (CSF) proteins are usually elevated in both these conditions and their response to immune-modulating treatments is substantial.^[10]

The EFNS guidelines on the treatment options of chronic inflammatory demyelinating polyradiculoneuropathies also suggests screening for paraproteins in all the patients diagnosed as CIDP and if the screening comes out to be positive then it must be labeled as paraproteinemia.^[11] The appropriate therapy for paraproteinemic neuropathies has yet to be established. Patients with IgA MGUS improve symptomatically within days or weeks after high-dose intravenous immunoglobulins (0.4 g/kg of body weight) daily for 5 days, a total of 4 to 5 plasma exchange sessions (a total of 220 ml/kg) or therapy with corticosteroids often in combination with immune-suppressants. Class I evidence documents plasma exchange to be effective in peripheral neuropathies associated with MGUS of the IgG and IgA, but not IgM, types.^[12] Another treatment is immunoabsorption, which is a blood purification

technique used to eliminate pathogenic antibodies but its role has not been fully proven through trials. Interferon alpha was also found to be beneficial in one trial.^[13] These treatment regimens produce only a transitory improvement and require recapitulation for several months depending upon the patient's response. If one treatment modality is unsuccessful, one may initiate an alternative modality which may lead to alleviation of symptoms. More studies are required to have a better understanding of the patho-physiology of various mechanisms involved and better biomarkers to ascertain the usefulness and efficacy of therapy.

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Waleed Shahzad; concept, data collection, data analysis, manuscript writing, manuscript review

Sumaira Nabi; data collection, data analysis, manuscript writing, manuscript review

Hafiza faiza Mushtaq; concept, data collection, data analysis, manuscript writing, manuscript review

Tehmina Inayat; data collection, data analysis, manuscript writing, manuscript review

Muhammad Hassan; data collection, data analysis, manuscript writing, manuscript review

Haris Majid Rajput; data collection, data analysis, manuscript writing, manuscript review