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Case report

Paraproteinemia associated Peripheral Neuropathy

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ABSTRACT

Peripheral Neuropathy can be acute or gradual over the years turning severe and quite debilitating to the patient. Diabetes, Alcohol or Drugs are some of the common causes of neuropathies however a small percentage of patients can present with paraproteinemia. The cause of paraproteinemia in these patients range from benign to serious malignant disorders such as Multiple Myeloma. We here report a case of an elderly patient who had to visit multiple center for over 4 months for his chronic neuropathy. Following extensive workup, he was started on an immunomodulating agent and glucocorticoids. Patient has remained free of disease and symptom free throughout treatment and thereafter.

Keywords: Paraproteinemia, MGUS, Peripheral Neuropathy

INTRODUCTION:

Peripheral neuropathy caused by disease, direct trauma or various systemic illnesses to peripheral nervous system results in numbness, tingling, burning pain, muscle weakness, lack of coordination and difficulty walking. The neuropathy could be serious and debilitating to an otherwise productive individual. The causes of neuropathy are diverse, but some of the patients with neuropathy could have rare etiologies such as monoclonal gammopathy. Most monoclonal gammopathies are non-malignant but in patients presenting with poly neuropathy, potentially serious malignant conditions must be explored which include multiple myeloma, solitary plasmocytoma, Waldenström's macroglobulinemia (WM), other IgM-secreting lymphoma or chronic lymphocytic leukemia, and primary systemic amyloidosis (AL) but in most instances it is not associated with any of these disorders and is defined as monoclonal gammopathy of undetermined significance (MGUS) however 17% to 25% of MGUS bearers may transform to one of the malignant disorders, over the course of 8-10 years. In this report, we report a case of Paraproteinemia associated Peripheral Neuropathy who was in diagnosis dilemma and improperly treated.

CASE REPORT

A 63 year old male patient visited various local hospitals with complaints of generalized body weakness and weight loss for 4 months at the end of 2013. Patient had undergone CABG 3 years before.The patient has no known history of diabetes or hypertension and was under medication for asthma and coronary artery disease. Generalized body weakness was associated with tremor, with difficulty in buttoning of shirts. There was no associated fever, sweating, shortness of breath, difficulty in walking, or thinning of limbs. Patient was a watch maker by profession and symptoms were quite debilitating. His complaints of neuropathy were assessed for myelinopathies, polyradicuolpathies, malignancies, and paraproteinemia with serum protein electrophoresis, immunofixation, serum free light chains, bone marrow aspiration and biopsy, skeletal survery for lytic lesions, routine hematology/biochemical parameters, CSF analysis, and EMG/NCS analysis. He was found to have normal hematological/biochemical profile. Bone marrow reported only 0.2% plasma cells with normal morphology and other cell lineages at normal phases of differentiation. Radiographic skeletal examination revealed no lytic lesions. SPEP was significant for monoclonal proteins, immunofixation analysis revealed

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monoclonal IgG heavy chain and kappa light chains. However Serum Free light chains showed normal ratios. Autoimmune markers such as ANA, ANCA were negative. CSF analysis useful in detecting myelinopathies and polyradiculopathies was normal; malignant cells were not detected. Using the data at hand a preliminary diagnosis of paraproteinemic neuropathy or Amyloidosis was made. Since patient was symptomatic and had a significantly increased secretion of monoclonal IgG k chains, patient was treated in the line of plasma cell dyscrasia with Lenalidomide at 15mg given in 21 days cycle with 7 days rest and Dexamethasone at 40mg given weekly for 4 weeks. During the course of treatment his neuropathy symptoms were better though he felt weak and increased in fatigue. His hematologic profile remain normal. After 6 months of therapy he was kept under maintenance lenalidomide and has been symptom free for last 2 years.

DISCUSSION:

Peripheral neuropathy caused by disease, direct trauma or various systemic illnesses to peripheral nervous system results in numbness, tingling, burning pain, muscle weakness, lack of coordination and difficulty walking. The neuropathy could be serious and debilitating to an otherwise productive individual. The causes of neuropathy are diverse, but some of the patients with neuropathy could have rare etiologies such as monoclonal gammopathy. Most monoclonal gammopathies are non-malignant but in patients presenting with poly neuropathy, potentially serious malignant conditions must be explored which include multiple myeloma, solitary plasmocytoma, Waldenström's macroglobulinemia (WM), other IgM-secreting lymphoma or chronic lymphocytic leukemia, and primary systemic amyloidosis (AL) but in most instances it is not associated with any of these disorders and is defined as monoclonal gammopathy of undetermined significance (MGUS) however 17% to 25% of MGUS bearers may transform to one of the malignant disorders, over the course of 8-10 years.

Immunoglobulins in monoclonal gammopathy is produced by a single clone of well differenetiated or progenitor B cell. The excessive protein and immunoglobulin present in these patients recognize and attack antigens present within the myelin sheath sometimes axons as well leading to demyelination and a variety of sensory and motor abnormalities which include pain, burning tingling,and muscle weakness. IgG and IgA are more commonly involved in Myeloma whereas IgM is most commonly associated with MGUS, B cell lymphomas and leukemias. However specific antibody activity in most monoclonal gammopathy can't be identified.

Monoclonal gammopathy in MGUS, B cell lymphomas and leukemias, POEMS and protein deposits due to Amyloidosis are more commonly involved with peripheral mono/polyneuropathy. The course of disease and response to therapy in paraproteinemic monoclonal gammopathy associated neuropathy is varied, so prognosis in this spectrum of disease can't be accurately defined and treatment strategy is aimed at remission of hematologic manifestations with immunosuppresants, immunomodulators, and ASCT.

Some studies indicate patients suffering from CIDP-like neuropathy with IgG MGUS doesn't necessitate a different therapeutic approach from CIDP without paraproteinemia. [2] Furthermore majority of patients with neuropathy associated anti-MAG IgM have a overall good prognosis for several years. Following 5 years of follow up, Mortality and increased disability in these patients were 8 and 16% respectively and mortality wasn't directly related to neuropathy. Interestingly mortality was higher in treated (37%) than untreated patients (17%), which reflects the higher frequency of haematological malignancy in treated (37%) than untreated patients (17%) and supports the rationale that treatment of underlying hematological malignancies could affect the overall survival of patients. [3] Plasma exchange is considered to be beneficial in IgG paraproteinemic neuropathy however the results are of modest benefit done over a short follow up.[4] Long term efficacy of Plasma exchange or other therapeutic measures in IgG neuropathy are not yet available. Furthermore comparision of IgM and IgG associated MGUS can't de differentiated clinically and half of the patients in both groups improve with immunotherapy.[4] Lack of substantial data especially congo red stain, quantitative monoclonal gammopathy and other cytogenetic information made it difficult to reach a definitive diagnosis in our patient. However LD regimen when started had substantial clinical benefit with disease in complete remission. We hence support treatment strategies aimed at controlling the underlying hematologic disease, patient has improved significantly following the therapy but whether treatment can be

stopped once the patient achieved complete remission for disease free status for a substantial number of years remains a question to be answered.

Summarising our brief report neuropathy can be interpreted as a manifestation of some commonly occurring disease such diabetes, B12 deficiency, alcohol abuse, leprosy. It is also commonly associated with monoclonal gammopathy. Such patients need early diagnosis and start of therapy since indolent disorders that fall in the spectrum of monoclonal gammopathy can take a very malignant course with time. However low risk MGUS are hardly recommended any treatment. Lenalidomide was initiated to relieve the patient of his debilitating symptoms which improved dramatically post treatment. There is yet no consensus on efficacy of Lenalidomide in such cases however clinical trials are studying the efficacy of Lenalidomide on treatment of neuropathy associated with MGUS.[5]

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