CASE REPORT

Waldenstrom's Macroglobulinaemia Presenting as Demyelinating Polyradiculoneuropathy

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Summary

Patients (particularly elderly) undergoing evaluation for peripheral neuropathy of unknown cause should be screened for the presence of a monoclonal protein (M protein). The association of a neuropathy and a paraproteinaemia such as Waldenstrom's macroglobulinaemia (WM) is not uncommon with the former antedating the haematologic symptoms by several years. Response to treatment has varied from good to very poor. We describe a case of WM presenting as a subacute demyelinating peripheral neuropathy. There was prompt resolution of the neuropathy with intravenous immunoglobulin therapy. Subsequent treatment with cyclophosphamide and plasmapheresis resulted in complete clinical remission with no further neurological relapses.

Key Words: Waldenstrom's macroglobulinaemia, Polyneuropathy, Monoclonal gammopathy, Intravenous immunoglobulin (IVIG)

Introduction

WM is an unusual low-grade lymphoplasmacytic lymphoma characterised by proliferation of malignant lymphocytoid cells in the bone marrow and lymph nodes that secretes monoclonal IgM. WM typically affects elderly men who usually present with systemic symptoms of fatigue, anaemia, bleeding and hyperviscosity. Peripheral neuropathy occurs in approximately one-third of patients with WM. Polyneuropathy associated with WM is usually of gradual onset, symmetrical and predominantly sensory[1]. However, in the present case, the associated polyneuropathy was subacute in onset, progressive and predominantly motor. This type of neuropathy in patients with WM is presumably very rare.

Case Report

A 78-year-old man was admitted with a three-week history of difficulty in walking. The weakness initially involved the lower limbs but

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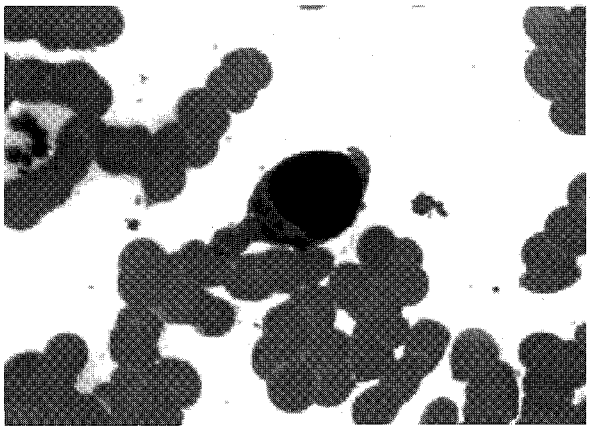

Fig. 1: Smear of the bone marrow aspirate (May-Grunwald-Giemsa,x400) showing a plasmacytoid lymphoid cell.

subsequently ascended to involve both upper limbs. There was no numbness, and no bladder or bowel incontinence. There was no history of fever or weight loss.

He had a history of forgetfulness for the preceding 2 years, and was treated as Alzheimer's disease with donepezil elsewhere. He did not have diabetes mellitus, hypertension or thyroid disorder. He was a non-smoker and teetotal.

Neurological examination revealed weakness in all four extremities; mainly affecting the distal muscles (power of grade 3-4 in the muscles of the shoulder and hip joints, grade 2-3 in the hands, wrist and ankle joints), and the flexors were weaker than the extensors. The deep tendon reflexes were absent. Both plantar responses were flexor. There was no muscle wasting, fasciculation or sensory deficit. The cranial nerves were normal. The lymph nodes, liver and spleen were not enlarged. Examination of other systems was unremarkable.

The haemoglobin level was 11.2 g/dl with normal red cell indices, white cell count 2.3 x 10^9/l and platelet count 259 x 10^9/l. Microscopic examination of the peripheral blood smears showed marked red cell rouleaux formation and leucoerythroblastosis. The erythrocyte sedimentation rate (ESR) was 124 mm in the first hour. The serum total protein level was 88 g/l, albumin 28 g/l, bilirubin 7 μmol/l, ALP 83 U/l and ALT 14 U/l. The blood glucose, serum electrolytes, serum creatine kinase and thyroid function test were normal and the VDRL was non-reactive. The bone marrow was heavily infiltrated by plasmacytoid lymphoid cells (Figure 1) and most of these cells expressed surface CD19, CD20 antigens and kappa light chains. No deposits of amyloid or cryoglobulin were observed in the trephine biopsy specimens. Serum protein electrophoresis revealed a raised IgM-kappa paraprotein level at 30.6 (NR: 0.5-2 g/l). The serum IgG level was 11.26 (NR: 5-14 g/l) and IgA 0.78 (NR: 0.5-3 g/l). A skeletal survey revealed no lytic lesions. The serum calcium level was normal. Serum β_2 microglobulin was elevated at 10.5 (NR < 3 mg/l). A diagnosis of Waldenstrom's macroglobulinaemia (WM) was made based on a high level of circulating IgM and bone marrow infiltration by plasmacytoid lymphocytes. The cerebrospinal fluid showed a slightly raised protein level of 537 mg/dl, normal glucose content and no cells or organisms. Nerve conduction studies disclosed prolonged distal motor and F-wave latencies, moderately diminished motor conduction velocities and reduced amplitudes of the sensory nerve action potentials. The findings were consistent with a symmetrical, predominantly motor, predominantly demyelinating polyradiculoneuropathy. The patient received intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for 5 days that resulted in marked improvement of his symptoms. He was able to walk with support on discharge. He also received oral chlorambucil 15 mg daily for one week (planned to be repeated every 4 weeks). However, he had two further similar neurological relapses within the next two months. He was treated with IVIG during both episodes of relapses with a similar favourable

response. His treatment was changed to 1 g of intravenous cyclophosphamide and plasmapheresis at 3-weekly intervals. After 3 courses of cyclophosphamide and plasmapheresis, the patient had no further neurological relapses and the paraprotein level had decreased to 8.4 g/l.

Discussion

Approximately 10% of patients with peripheral neuropathy of otherwise unknown aetiology have an associated monoclonal gammopathy, and approximately one third of patients with WM develop a chronic, predominantly demyelinating sensory polyneuropathy[1]. This patient's initial clinical presentation did suggest a diagnosis of Guillain-Barre Syndrome (GBS), and the polyneuropathy was subacute in onset and predominantly motor. This type of neuropathy is uncommon in patients with WM. Sural nerve biopsy findings of patients with M proteins show nerve fibre loss, segmental demyelination, and axonal degeneration, but nerve biopsy was not performed in the present case, as it would not differentiate benign monoclonal gammopathy from malignant plasma cell dyscrasias. Immunocytochemical studies on sural nerve biopsies have shown that the monoclonal IgM (usually of κ type) is deposited on the outer layer of the myelin sheath, a sign suggestive of IgM anti-myelin antibody activity. IgM M proteins that bind to myelin-associated glycoprotein (MAG) have been shown to cause demyelinating peripheral neuropathy. Anti-MAG reactivity is found in 50% of WM patients with neuropathy[1]. In this case, anti-MAG reactivity was not done, as the test was not available.

The management of polyneuropathy associated with monoclonal gammopathy relies on the administration of systemic chemotherapy to reduce tumour load and on the application of plasmapheresis to remove circulating IgM. The effectiveness of these treatment modalities remains uncertain. The most difficult cases to treat are those with peripheral neuropathies associated with IgM monoclonal gammopathies. Plasma exchange, followed by a course of chlorambucil is indicated if the symptoms and signs are predominantly sensory. For cases with rapid progression or significant disability, a regimen of monthly pulses with cyclophosphamide is recommended[2]. In a prospective study, short-term treatment with intermittent cyclophosphamide and prednisone can prevent worsening of neuropathy associated with monoclonal gammopathy of undetermined significance (38%) or lead to amelioration (50%), and a reduction in the M-protein levels [3]. Our patient was initially treated with IVIG based on the provisional diagnosis of GBS. However, no studies have been done so far to prove the effectiveness of IVIG in the treatment of polyneuropathy associated with WM. This patient had two episodes of neurological relapses with a consistent favourable response to IVIG, suggesting the efficacy of this treatment, albeit an expensive one. Subsequent treatment with cyclophosphamide and plasmapheresis resulted in both neurological and haematological remission.

This case illustrates the importance of investigating for a paraproteinaemia in elderly patients who present with a subacute peripheral neuropathy, particularly when it mimics GBS, and in the presence of a high ESR or elevated total protein level. It is particularly important to recognise the underlying malignant paraproteinaemia because treatment of these diseases may result in amelioration of the neuropathy and remission of the underlying malignancy. In addition, electrophysiological studies are pivotal in the diagnostic evaluation of patients who present with a clinical diagnosis of peripheral neuropathy, and polyneuropathy associated with monoclonal gammopathy can be treated effectively with IVIG and cyclophosphamide.

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