

Acute Acquired Demyelinating Polyneuropathy: An Initial Presentation of Diffuse Large B Cell Lymphoma

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Abstract

Neurological signs and symptoms are commonly associated with both Hodgkin's and non-Hodgkin's lymphoma and are mostly attributed to either direct lymphomatous involvement of the nervous system, either as a result of extension to the spinal cord or nerves, or due to infiltration by lymphoma cells and drug toxicity. Guillain-Barre syndrome and its variants have been reported very infrequently in the literature. We present the case of a 70-year-old male admitted to the hospital for evaluation of uncontrolled hypertension. Incidentally, he was noted to have a low platelet count and a leukoerythroblastic picture in the peripheral blood. Two days into admission, he developed bilateral symmetrical ascending paresis consistent with acute acquired demyelinating polyneuropathy, a common variant of Guillain-Barre syndrome. At about the same time he developed worsening cytopenia and was diagnosed with diffuse large B cell lymphoma according to a bone marrow biopsy. The patient was treated with intravenous immunoglobulin for Guillain-Barre syndrome with significant improvement in muscle strength and subsequently treated with chemotherapy for his lymphoma.

Keywords: Guillain-Barre syndrome, Diffuse large B cell lymphoma, Initial presentation, Intravenous immunoglobulin

Introduction

Peripheral neuropathies are a very rare presentation of lymphoma which may result from direct infiltration of the nerves by lymphoma cells, neuropathies that result from paraneoplastic phenomena, and acute and chronic demyelinating neuropathies. Acute demyelinating neuropathy, also known as Guillain-Barre Syndrome (GBS), has been

reported to have a more frequent association with Hodgkin's lymphoma. It is, however, a very rare presentation of non-Hodgkin's lymphoma (NHL). We present the case of an elderly male with diffuse large B cell lymphoma in whom GBS was the initial presenting sign. Recognition of GBS as paraneoplastic manifestation of lymphoma and subsequently GBS-

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directed treatment led to improvement in the patient's neurological deficit.

Case report

A 70-year-old gentleman presented to the emergency room with a three-week history of progressively worsening headaches and elevated blood pressure. Past medical history was significant for diabetes mellitus, hypertension and a 100 pack-year history of cigarette smoking. Review of systems did not reveal any antecedent infections or other illnesses. A detailed physical examination was unremarkable. He was subsequently admitted to the hospital for further work up and management. Initial laboratory tests were essentially normal, except for the mild thrombocytopenia noted in the complete blood counts (CBC). CBC analyses revealed hemoglobin (Hb) 12.5 g/dL (11.1-14.5 g/dL), white blood cell count (WBC) 10200 mm^3 ($4.9-10.0 \times 10^9/\text{L}$) with a normal differential, platelet count $113,000 \text{ mm}^3$ ($150-400 \times 10^9/\text{L}$) and lactate dehydrogenase (LDH) 1109 U/L (266-500 U/L). Peripheral blood smear was significant for nucleated RBCs, left shifted myelopoiesis with increased numbers of myelocytes and metamyelocytes consistent with a leukoerythroblastic picture. Serum prostatic specific antigen (PSA) was within normal limits. Serum protein electrophoresis with immunofixation revealed no evidence of monoclonal gammopathy. Bence-Jones proteins were qualitatively absent from the urine. Corrected serum calcium was normal. Magnetic resonance imaging (MRI) of the brain revealed widening of the diploic space in the frontal region which was hypointense on T1 and hyperintense on T2. CT scans of the chest, abdomen and pelvis showed no evidence of malignancy, organomegaly or lymphadenopathy. Subsequently a bone marrow aspirate and biopsy was performed for evaluation of mild thrombocytopenia and the leukoerythroblastic picture seen in the peripheral blood film.

On the third day of admission, the patient developed sudden onset of generalized weakness. Thereafter, he began to complain of symmetrical ascending Parasthesias and worsening dyspnea. A detailed neurological examination revealed no

cognitive deficits and a normal cerebellar function. Cranial nerve examination was within normal limits. Motor examination was significant for symmetrical flaccid quadriparesis with diminished strength and reflexes. Sensory examination was significant for bilaterally decreased sensation. CT scan of the head was within normal limits. Lumbar puncture and cerebrospinal fluid analysis revealed glucose of 86 mg/dL (50-75 mg/dL), protein 36 (15-45 mg/dl), and leukocyte count of 2 cells/mm³ (0-6 cells/mm³). Gram stain was negative for pus cells and microorganisms.

Subsequently, the patient underwent nerve conduction studies (NCS) two days after the onset of his symptoms. NCS evaluation revealed undetectable H reflexes, prolonged distal motor latencies in the right tibial, right ulnar and bilateral median nerves with evidence of a conduction block in the right tibial nerve. Mild slowing of conduction velocities was noted in the lower extremities. Only the radial nerve action potential (SNAP) was recordable bilaterally. Electromyography (EMG) showed no evidence of denervation. Based on the electrophysiological studies the diagnosis of early acute acquired demyelinating polyneuropathy, one of the common variants of GBS was given.

Follow-up laboratory analyses were remarkable for progressive worsening of biochemical parameters and blood cell counts. LDH increased from 1109 U/L at admission to a peak of 15462 U/L. He also developed worsening thrombocytopenia, leukopenia and anemia reaching a nadir of 6000 mm^3 , 640 mm^3 , and 6.8 g/dl, respectively. The patient's respiratory status deteriorated steadily; eventually he required intubation and mechanical ventilation on the eighth day of admission, which was five days after the onset of his weakness. With the diagnosis of GBS, he was subsequently started on intravenous immunoglobulin (IVIG) at a dose of 1g/kg. He responded well to a five-day course of IVIG with marked improvement in his muscle strength and was subsequently successfully extubated, three days post-intubation.

Biopsy of the bone marrow aspirate was significant for diffuse infiltration of mononuclear cell clusters with basophilic cytoplasm and prominent vacuoles. Marrow was hypercellular for age (70%-

Table 1. Reported cases of patients with lymphoma developing unexplained neuropathy.

Age (yrs.)	Disease	Response to treatment with IVIG/plasmapheresis	Reference
61	Diffuse large B cell lymphoma	Yes	[11]
55	Intravascular B cell lymphoma	No	[12]
78	Intravascular B cell lymphoma	No	[9]
26	B cell ALL	Responded to treatment of ALL	[13]
6	CNS Burkett's lymphoma	No response to IVIG but complete resolution with the treatment of lymphoma	[10]

Abbreviations: ALL: Acute lymphoblastic lymphoma; CNS: Central nervous system; IVIG: Intravenous immunoglobulin

75% cellularity) with interstitial and paratrabecular infiltration of mononuclear cells. Immunohistochemical and flow cytometry analyses for myeloid and lymphoid markers showed positive B-lymphoid markers CD 79a, CD 19, CD 20, CD 22, surface IgM and lambda light chain restriction and negative for CD 10 and lymphoid T markers as well as myeloid markers. FISH for translocation (8:14) was negative. The findings were consistent with a B cell NHL and favored diffuse large B cell lymphoma.

The patient was subsequently treated with combination chemotherapy with rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) on the 8th day of admission. Clinically, he continued to have improvement in muscle strength. Laboratory values showed significant improvement, with a significant decline in LDH and increments in WBC and platelet counts. He was subsequently discharged on the 17th day after admission on prophylactic antimicrobials. However, he was re-admitted a few days later with low grade fever, cough and shortness of breath. Labs revealed pancytopenia consistent with febrile neutropenia. There was a significant worsening of his muscle strength as a result of which he was re-intubated for impending respiratory failure. ICU course was complicated with septic shock due to *Pseudomonas aeruginosa*. Despite maximal support, the patient developed multi-organ system failure and died.

Discussion

Guillain-Barre syndrome is a heterogeneous disease which has variant forms. Most commonly it presents as an idiopathic acute inflammatory demyelinating polyneuropathy which is thought primarily to be immunologically mediated. In a

significant proportion of cases a predisposing factor can be elicited. This could be an antecedent respiratory or gastrointestinal tract infection particularly attributed to *Campylobacter jejuni*, cytomegalovirus and Epstein-Barr virus, history of recent vaccinations and systemic diseases, such as human immunodeficiency virus infection and systemic lupus erythematosus. The classic presentation is Parasthesias in the toes and fingertips followed by lower extremity symmetric weakness that may ascend over a period of hours to days involving the arms and, in severe cases, the respiratory muscles. More than 90% of patients reach the nadir of their function within two to four weeks followed by slow improvement in function that can take from a few weeks to months. To confirm the diagnosis of GBS, NCS and CSF analysis are routinely performed.¹

It is not uncommon for patients with lymphoma to develop neurological abnormalities. Significant clinical scenarios in the differential diagnosis for such patients include cord compression due to external compression by a nodal or extra nodal lymphoma, nervous system infiltration by lymphomatous cells manifesting as nerve palsies and drug toxicity as seen with cytarabine, vinca alkaloids and intrathecal methotrexate.²⁻⁴ Guillain-Barre syndrome is a very rare neurological finding in patients with lymphoma. A well-documented association between GBS and Hodgkin's lymphoma exists.⁵ However, this is far more infrequently reported with NHL with an estimated occurrence in less than 0.3% of patients.³

In the majority of cases reported in the literature, patients diagnosed with lymphoma and co-incidental demyelinating neuropathy had also

received potentially neurotoxic chemotherapy regimens^{3, 4, 6-8} which could have caused or exacerbated their symptoms. Guillain-Barre syndrome in patients with lymphoma in the absence of confounding factors has been very infrequently reported. Despite an exhaustive literature search we were only able to find six case reports in which the development of neuropathy could not be explained by any other cause (Table 1).⁹⁻¹³ Additionally; the diagnosis of GBS preceding the diagnosis of lymphoma is very rare. Our case is unique as it is one of the few cases that have been reported in which GBS was the initial presentation for NHL. The diagnosis of GBS in our patient was supported by the clinical picture and typical findings on NCS of absent H reflexes, prolonged distal latencies and mildly prolonged conduction velocities, which are characteristic for GBS.

Plasma exchange and IVIG are the standard of care for management of GBS. Although plasma exchange (PE) has been considered as the gold standard, randomized controlled trials have shown that IVIG is at least as effective.¹⁴ Expert opinions from the American Academy of Neurology (AAN) also endorse the equal efficacy of PE and IVIG and affirm the lack of benefit in combining these two treatment modalities. The literature suggests that response to GBS directed treatment is very variable and there are no predictive factors to aid in directing the therapeutic management. Despite this uncertainty in response, PE and/or IVIG are usually the first line treatments in the management of GBS associated with lymphoma. We have used this strategy and our patient responded very well to IVIG with a rapid improvement in his neurological symptoms.

In summary, we reported the case of an elderly gentleman with stage IV diffuse large B cell lymphoma who presented with GBS and had rapid improvement of his symptoms following treatment with IVIG. Treatment of the underlying lymphoma resulted in additional improvement in muscle strength.

Neurological manifestations of lymphoma are varied and usually multifactorial. However GBS is a rare event in lymphoma and needs to be considered in patients who develop acute sensory motor

neuropathy. Prompt initiation of GBS-directed treatment with either PE or IVIG is an essential first step in treatment as early resolution has been implicated in decreasing morbidity and mortality.

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