Unusual neurological presentations resulting in diagnosis of lymphoma in three patients

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ABSTRACT

Nervous system involvement affects up to one-third of patients with lymphoma, via a variety of mechanisms ranging from direct invasion to demyelination, paraneoplastic processes, and treatment-related complications. Nervous system involvement can manifest at any location and occur at any stage of lymphoma, often resulting in distinct and atypical patterns. Here we describe three patients, presenting each with motor predominant polyradiculoneuropathy and cranial neuropathy, transient encephalitis, and frontal gait dysfunction. Through further workup, all were diagnosed with lymphoma, with their neurological manifestations directly or indirectly related to the underlying lymphoma. Our study serves as an alert that in patients presenting with unusual neurological symptoms, lymphoma should be a consideration on the differential diagnosis.

Keywords: lymphoma, polyradiculopathy, encephalitis, frontal lobe dysfunction, PET

Introduction

A variety of neurological complications are associated with lymphoma that can variably arise at different stages of malignancy and in different locations of the nervous system.[1-8] The mechanisms underlying the nervous system involvement are diverse, including direct lymphomatous invasion of the central nervous system parenchyma or peripheral nerves, paraneoplastic/immune-mediated damage, demyelination, vascular dysfunction, therapeutic intervention related neurotoxicity, metabolic derangement, and opportunistic infection.[7,9-11] The existing diversity in the underlying mechanisms, the difference in timing of occurrence, and the heterogeneity in involved location often render the diagnosis of lymphoma difficult. In this case series, we describe three patients that highlight the variability in neurological patterns as the presentation of underlying lymphoma.

Patient 1

A 65-year-old male with a history of hypertension and nephrolithiasis presented with symptoms of bilateral hand weakness and numbness for one month, and blurred vision and slurred speech over two days. The numbness mainly involved the last two fingers of each hand and the medial forearms. There was also a 10-pound weight loss, myalgia, and arthralgia in the preceding month, and analysis of peripheral blood count revealed persistent eosinophilia. Initial rheumatological and hematological evaluations did not lead to a definitive diagnosis, and a bone barrow biopsy was unremarkable. At presentation, his cranial nerve exam showed intact eye motility, moderate weakness in the bilateral orbicularis oculi, bilateral lower facial weakness, and mild flaccid dysarthria. Muscle strength exam revealed the following (right/left, Medical Research Council Scale): shoulder abductors 5/5, elbow flexors 5/5, elbow extensors 5/5, first dorsal interossei 3/4, abductor digitorum minimi 4/5, hip flexors 5/5, knee extensors 5/5, knee flexors 5/5, dorsiflexors 5-/4, planter flexors 5/4, evertors 5/4, and invertors 5/4. Findings on tendon reflex examination were as follows: bilateral biceps reflexes were hypoactive, triceps reflexes normal, bilateral knee and right ankle jerks absent, and left ankle jerk normal. No clear sensory deficits were observed. Based on the clinical examination, it was felt that the patient may have an acute to subacute asymmetrical motor more than sensory polyneuropathy or polyradiculoneuropathy. Electrodiagnostic (EDX) study confirmed the presence of a motor predominant polyradiculoneuropathy that affect cervical, thoracic and lumbar segments. No significant demyelination was found on nerve conduction studies. Brain MRI revealed contrast enhancement of the distal canalicular segments of cranial nerves VII and VIII bilaterally (Figure 1). No significant contrast enhancement was observed on MRI of the cervical, thoracic, and lumbar spine segments. Cerebrospinal fluid (CSF) studies revealed the following: protein 95 mg/dl, glucose 60 mg/dl, and white blood cell 3 per microliter.

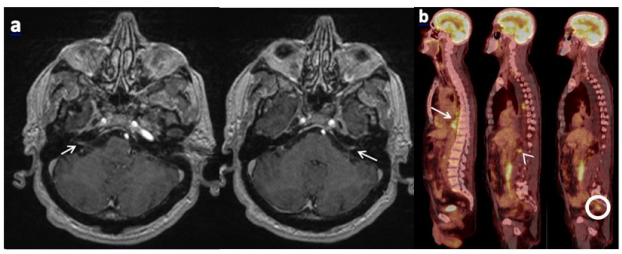

Figure 1. Image findings in patient 1. (a) MRI of the brain with contrast showed bilateral, distal enhancement of cranial nerves VII and VIII within the internal auditory canals.; (b) PET CT showed FDG avid lesions in posterior mediastinal (arrow), retroperitoneal (arrowhead), and pelvis (circle).

CT scan of chest, abdomen and pelvis showed multifocal lymphadenopathy. Whole body PET scan showed multifocal fluorodeoxyglucose (FDG) avid lesions involving the posterior mediastinum, retroperitoneum, and extra peritoneal spaces in the pelvis (Figure 1). A retroperitoneal node biopsy confirmed the diagnosis of a T-cell lymphoma. Flow cytometry analysis confirmed the presence of T cell lymphoma cells in CSF. The patient was initially treated with intravenous immunoglobulin (IVIG) which led to minimal improvement. His condition was stabilized with further chemotherapy treatment consisting of CHOP plus intrathecal methotrexate.

Patient 2

A 51-year-old-male with history of lumbar spine degeneration presented with acute headache, nausea, vomiting, confusion, and poor balance, notably without fever. Three weeks prior, he had signs of sinus congestion and nasal drainage, treated with amoxicillin and pseudoephedrine. On exam he was noted to have fluctuating level of consciousness, transient right gaze preference, and left sided neglect. CT angiogram of the cerebral vessels was normal. Brain MRI with and without contrast were unremarkable. Bedside EEG monitoring for 24 hours showed no epileptiform discharges. CSF study revealed the following: protein 98 mg/dl, glucose 52 mg/dl, and white blood cell 193 per microliter (lymphocytes 92%). Numerous studies to evaluate for infection resulted negative including human immunodeficiency virus screening. He was started on a treatment regimen of ceftriaxone, vancomycin, ampicillin, acyclovir, and dexamethasone with rapid and dramatic improvement in his condition. A repeat CSF study the day after presentation revealed the following: protein 88 mg/dl, glucose 74 mg/dl, and white blood cell 8 per microliter (lymphocyte 74%). It was felt that he likely had lymphocytic meningitis of a viral etiology, and he was discharged without further antibiotics or corticosteroid treatment.

Three days following discharge, his symptoms of headache, nausea and vomiting, neck stiffness, and gait instability returned. He was readmitted two weeks following discharge. On exam, he was found to have speech delay, deficits in attention and performing calculations, and gait ataxia. A third CSF study revealed the following: protein 86 mg/dl, glucose 45 mg/dl, and white blood cell 5 per microliter (lymphocyte 29%, monocyte 70%). CSF cytology and flow cytometry were negative. Clinical concern was raised for possible autoimmune encephalitis. Autoimmune encephalitis antibody panels via Mayo Clinic were negative in both serum and CSF. Brain PET scan did not reveal evidence of autoimmune encephalitis. PET scan of the body revealed an FDG-avid process in the lungs, brain, kidney, spleen, and bone marrow (Figure 2). Bone marrow biopsy of the right posterior superior iliac crest and biopsy of the left kidney confirmed the diagnosis of a diffuse large B cell lymphoma. He was treated with R-CHOP therapy. Six weeks following the diagnosis and treatment of lymphoma, his neuralogic examination had improved, though the wide-based gait persisted.

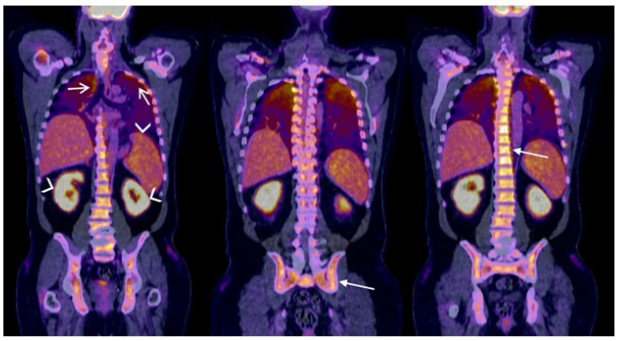

Figure 2. Image findings in patient 2. PET CT showed FDG avid lesions in bilateral lung (open-head arrows), bilateral kidney and spleen (arrowheads), and bone marrow (closed arrows).

Patient 3

A 63-year-old male presented with difficulty walking, leg heaviness, and left-sided headache. Over several years prior to presentation, his walking had gradually become slower with shorter distances traveled. His major concern was inability to pick up his legs high, stating "my brain tells me not to walk." On physical exam, muscle strength was normal. He demonstrated difficulty in raising his legs up while sitting but could do it well while lying down. A slightly wide-based gait was observed. EDX studies did not show evidence of a large fiber polyneuropathy or lumbosacral radiculopathy. Lumbar spine MRI was unremarkable. Brain MRI revealed an overlying extracranial soft tissue mass involving a large portion of the left greater than right frontoparietal, extra-skeletal calvarium with underlying marrow replacement and associated mild pachymeningeal thickening resulting in subtle signal changes in the underlying brain parenchyma on FLAIR sequence (Figure 3). Concerns for an intraosseous meningioma versus slow-growing metastasis or myelomatous lesion were raised. CSF study revealed the following: protein 32 mg/dl, glucose 58 mg/dl, and white blood cells 2 per microliter, with normal CSF cytology. Further PET scan revealed FDG avid left frontoparietal scalp/subcutaneous soft tissue thickening without significantly increased FDG activity in the underlying calvarium (Figure 3). No FDG avid lesions

were observed in the brain parenchyma or other regions of the body. A left frontal scalp biopsy confirmed the diagnosis of small B-cell lymphoma. Bone marrow biopsy was normal. Radiation treatment to the scalp was initiated.

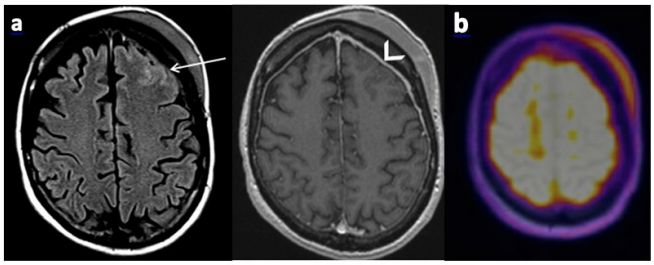

Figure 3. Image findings in patient 3. (a) MRI of the brain showed the left frontal scalp mass with underlying frontal lobe compression and FLAIR hyperintense changes (arrow) and left greater than right pachymeningeal thickening and enhancement (arrowhead) on post-contrast T1 sequence; (b) Brain PET FDG avidity in left frontal soft tissue scalp.

Discussion

Nervous system involvement in lymphoma is frequent and may affect up to one-third of patients. [4,7,9] The clinical presentation of lymphoma affecting the nervous system varies widely depending on the site of involvement. Typical central nervous system complications include intracranial or intramedullary metastases, leptomeningeal metastases, limbic encephalitis, paraneoplastic cerebellar degeneration, and primary central nervous system angiitis. Classical involvement of the peripheral nervous system includes subacute to chronic mononeuropathies, radiculopathies, plexopathies, cranial neuropathies, symmetrical axonal polyneuropathy, mononeuritis multiplex, and demyelinating polyneuropathy mimicking Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP). Given the myriad timing, location, and pathophysiological mechanisms underlying these conditions, the presentation of nervous system involvement in lymphoma may be atypical, not fitting well to any of the classical presentations of the above-mentioned diagnoses.

Our patient 1 presented with subacute motor and sensory symptoms that affected the craniobulbar region and limbs. Further workup indicated the presence of cranial neuropathy and asymmetrical, motor-predominant polyradiculoneuropathy. His EDX study did not reveal evidence of demyelination. Further treatment with IVIG did not lead to significant improvement. No nerve root enhancement was observed on spinal MRI. Therefore, it is unlikely that he suffered from acute inflammatory demyelinating polyradiculoneuropathy (AIDP, GBS) or CIDP. Flow cytometric analysis confirmed the presence of T cell lymphoma in his CSF, making leptomeningeal lymphomatosis a distinct possibility. We cannot rule out a diagnosis of neurolymphomatosis due to a lack of nerve biopsy.

Our patient 2 presented with a multitude of symptoms that were concerning for a form of encephalitis. However, his presentation lacked the typical features of limbic encephalitis. On MRI and PET scan, there was a lack of mesial temporal lobe and amygdala involvement. No clinical or electrographic seizures were observed. CSF study initially showed prominent pleocytosis, but this quickly resolved. Autoimmune antibody panel testing in the serum and CSF was normal. The patient improved quickly with a short course of corticosteroids, and subsequently with the treatment of the discovered, underlying lymphoma. This supports the neurological symptoms as being associated with the underlying lymphoma, possibly through immune-mediated mechanisms resulting in the appearance of an aseptic meningoencephalitis on initial testing and evaluation.

Our patient 3 presented with headache and a gait disorder that seemed to suggest frontal lobe dysfunction. His evaluation was remarkable for the presence of a frontal scalp lesion that affected the underlying meninges and frontal lobe. Oncologic evaluation showed histopathologic and genetic abnormalities consistent with small B-cell lymphoma. The diagnosis of lymphoma in this case was surprising; the origin of this lymphoma as being extracranial or intracranial remains unclear.

In all three patients, FDG-PET scan was invaluable in supporting or leading to a diagnosis of lymphoma. Therefore, we feel that such diagnostic scans should be considered in patients with atypical neurological presentations where lymphoma is in the differential diagnosis.

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