A Diagnosis Dilemma of Back Pain in Non-Hodgkin's Lymphoma

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Abstract

Introduction: CNS metastasis is a serious, and often fatal, complication of non-Hodgkin lymphoma (NHL). Accurate diagnosis and prompt treatment of this condition are essential for providing symptomatic relief, preserving neurologic function, and improving survival.

Method: We report a case of a 19-year-old woman with mediastinal B-cell lymphoma who presented to hospital with severe lower back pain. Lumbar punctures proved to be difficult to perform and multiple CSF analyses were persistently negative for malignant cells. A brief review of published literature will be performed on the efficacy of CSF cytologic examination in the diagnosis of leptomeningeal lymphomatosis.

Results: To our knowledge, there are no additional reports in the world literature rivaling the magnitude of diagnostic difficulty encountered in our case.

Conclusion: The low sensitivity of CSF cytologic analyses continues to make the diagnosis of leptomeningeal metastasis a very challenging one. Patients presenting with back pain may also make lumbar punctures technically difficult to perform. In such instances, neuro-imaging studies such as MRI may be a useful diagnostic adjunct. Further study into new diagnostic approaches with the aim of improving recognition of leptomeningeal disease would be invaluable.

ABBREVIATIONS

CNS – central nervous system,
NHL – non-Hodgkin's lymphoma,
CSF – cerebrospinal fluid,
MRI – magnetic resonance imaging

INTRODUCTION

Secondary lymphomatous involvement of the central nervous system was first documented by Murchison in the early 19th century ([1]). Although relatively uncommon, central nervous system metastasis is a serious complication seen in patients with cancer. Accurate diagnosis and prompt treatment of this condition are essential for providing symptomatic relief, preserving neurologic function, and improving survival. While any cancer has the potential to metastasize to the leptomeninges, it occurs most often in patients with hematological malignancy and is invariably associated with considerable morbidity and mortality ([2]). With the advent of more effective therapy against primary lymphoma in the past several decades, the natural history of lymphoma has been prolonged. As a result, the incidence of secondary central nervous system lymphomas has increased ([3]).

CASE HISTORY

A 19-year-old woman with stage II, intermediate grade, mediastinal B-cell non-Hodgkin's lymphoma (NHL) presented with a 10-day history of progressively worsening back pain accompanied by lower extremity weakness and paresthesia. Further questioning revealed a history of constipation and urinary retention that began approximately one week prior to presentation. The patient's NHL was diagnosed six months earlier; she subsequently underwent four cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, followed by a relatively uncomplicated clinical course. She completed her last dose of chemotherapy two weeks ago.

The patient was afebrile and normotensive. Findings of the

cardio-pulmonary and abdominal examination were unremarkable. Examination of the back revealed marked tenderness along the L4 to S1 vertebrae. There was no erythema, swelling, or deformity. Neurological examination showed decreased strength and diminished reflexes bilaterally in the lower extremities, but was otherwise normal. There was no meningismus. Digital rectal examination demonstrated normal anal tone.

Complete blood count revealed a decreased white blood cell count of 2,700/uL with neutrophils measuring at 1,500/uL. Electrolytes, renal and liver function tests, and electrocardiogram were non-contributory. Given the patient's neurological complaints, a computed tomography (CT) scan of the brain and of the lumbar spine were performed; findings were normal. Imaging of the chest, abdomen, and pelvis were also performed and were unremarkable. Because of the patient's history of NHL, there were grave concerns regarding the possibility of lymphomatous invasion into the central nervous system. Therefore, a T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) study of the spine was done; results of this initial test did not support the diagnosis of leptomeningeal disease. A lumbar puncture performed on admission did show elevated protein (2.38g/L) and low glucose (0.3mmol/L) levels in the cerebrospinal fluid, but was otherwise normal. Meanwhile, the patient experienced progressive paresthesia and weakness in both feet and worsening back pain. She also developed mild confusion and some disorientation, which were partly attributed to the opiates she was receiving to control her back pain. Considering the patient's neurologic deterioration, she received empiric therapy with high-dose dexamethasone, methotrexate, intrathecal cytarabine, and local spinal irradiation for presumptive meningeal lymphomatosis.

Twelve days after the initial presentation, a repeat T1-weighted gadolinium MRI study (Fig 1B), compared to a normal scan (Fig 1A), showed substantial enhancement from T8 to L5 (indicated by white arrows), consistent with a diagnosis of extensive lymphomatous involvement of the spine. Despite attempts from four different anesthesiologists, multiple lumbar punctures to obtain cerebrospinal fluid for further analyses were unsuccessful. The patient consistently reported shooting pain radiating down her legs as the lumbar puncture needle was advanced into her back. When this occurred, the lumbar puncture was aborted. Attempts under general anesthesia and fluoroscopic guidance were similarly unsuccessful. Ultimately, an Ommaya reservoir was placed to retrieve samples of the patient's cerebrospinal fluid. Results of all CSF cytologic examination were remarkably normal and consistently negative for malignant cells.

Shortly after empiric treatment was initiated, the patient's back pain improved. However, her lower limb weakness and numbness remained unchanged. Unfortunately, the patient's clinical response was only transient. Several weeks after therapy, she developed progressive neurologic impairment involving the upper limbs. She also complained of difficulty swallowing. Repeat CSF analyses were negative, but repeat MRI did show progression of disease rostrally to the cervical spine. Given the neurologic progression, palliative care was consulted and the patient and family were informed of the grim prognosis.

The patient ultimately expired secondary to complications from NHL. Autopsy revealed B-cell NHL involving the cerebellar leptomeninges (Fig 2A and 2B) with extensive spinal nerve root destruction. Lymphoma was not identified in the lower spinal cord, although this area was marked by substantial fibrosis and destruction of spinal nerve roots (Fig 3). Fibrosis is not a typical manifestation of malignant invasion into nervous tissue. As such, this case may possibly represent a necrotic reaction induced by radiotherapy or chemotherapy.

Figure 1

Figure 1A: MRI of normal lumbar spine (indicated by arrows). Figure 1B: MRI of the lumbar spine demonstrating enhancement from levels T8 to L5 (indicated by arrows), consistent with leptomeningeal disease

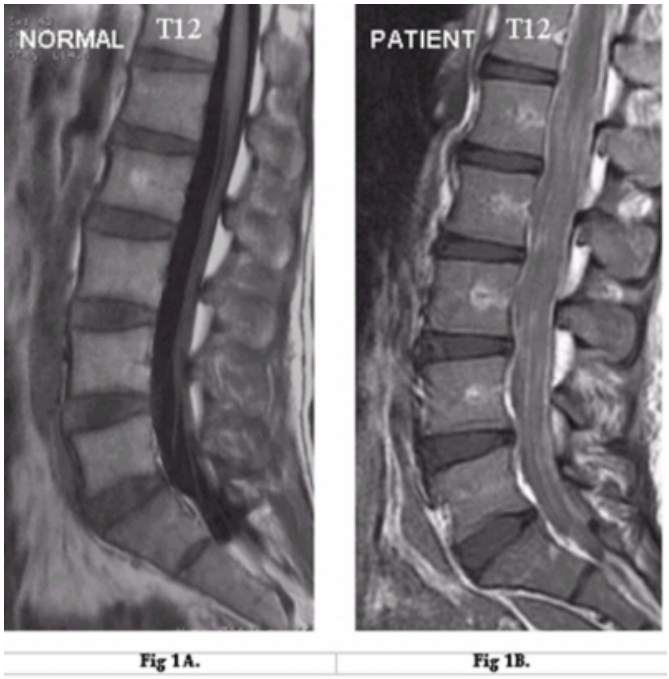


Fig 1A. Fig 1B.

Figure 2

Figure 2A: Predominance of B-cell lymphocytes in the subarachnoid space of the cerebellar leptomeninges. Figure 2B: CD20 staining highlights the predominance of B-cell lymphocytes

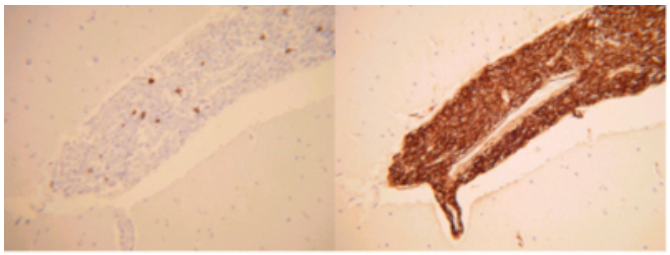
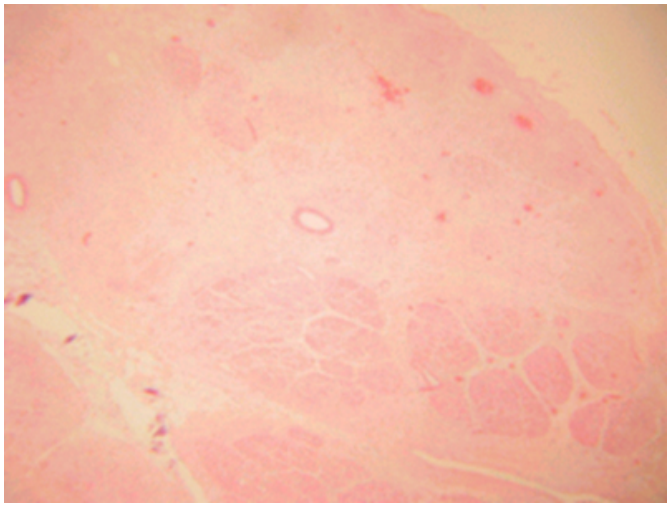


Fig 2A. Fig 2B.

Figure 3



DISCUSSION

The clinical manifestations of leptomeningeal disease are variable. Features may include mental status changes, headaches, cranial nerve palsies, spinal compression, back pain, sensory or motor deficits, and radicular pain ([4]). Nevertheless, the diagnosis of leptomeningeal disease is based on the gold standard of detecting malignant cells in the cerebrospinal fluid during cytologic examination ([5]). A MEDLINE review of published literature between 1966 and 2004 did not reveal any reports rivaling the magnitude of diagnostic challenges encountered in this patient. Although earlier studies have commented on the limited sensitivity of cytologic analysis of cerebrospinal fluid ([6], [7]), our case is notable for the difficulty and failure to obtain cerebrospinal fluid despite multiple attempts, expert techinique (by anesthesiologists), and radiologic guidance. Glantz et al ([8]) previously found that false-negative results from cerebrospinal fluid cytology could be minimized by performing another lumbar puncture. Olson et al ([9]) supported this finding, and reported the sensitivity of a single spinal tap and after multiple taps as 45% and 80% respectively. Interestingly, in our case, repeated examinations remained persistently negative for malignant cells. Moreover, initial magnetic resonance imaging was not of particular value in the prompt diagnosis of leptomeningeal disease in our patient. Of note, the diagnosis ultimately rested on a repeat MRI study performed 12 days following initial presentation.

Lymphomatous involvement of the central nervous system should be suspected in any non-Hodgkin’s lymphoma patient who experiences back pain, sensory or motor deficits, or altered mental status. The recognition of neoplastic cells

in the cerebrospinal fluid is classically considered the most important diagnostic criterion. Nevertheless, neuro-imaging studies are an important diagnostic adjunct for leptomeningeal disease, as demonstrated in this case ($_{10}$). However, the clinician should be cognizant of the limitations of these techniques. In our scenario, obtaining cerebrospinal fluid proved to be complicated and problematic. If the clinical presentation is convincing, the patient should promptly receive systemic and intrathecal chemotherapy to abate the disease. In our patient, her progressive neurologic deterioration necessitated treatment without delay. MRI findings ultimately supported our decision to treat the patient. Unfortunately, the patient's clinical status was too grave, and she subsequently expired secondary to her neurologic complications.

CONCLUSION

This interesting case illustrates two important points. First, the low sensitivity and challenges of cerebrospinal fluid cytology and neuro-imaging studies continue to make the diagnosis of leptomeningeal metastasis a very difficult one. Further study into new diagnostic approaches with the aim of improving recognition of this clinical entity would be invaluable. Second, neurologic deficits from central nervous system metastasis are frequently irreversible and associated with a poor prognosis. Until more effective diagnostic modalities are developed, a high index of suspicion and early intervention are critical to improving patient outcome.

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