Spinal Leptomeningeal Lymphoma Presenting as Pseudotumor Syndrome

Rebekah M. Ahmed, MBBS, John King, MD, FRACP, John Gibson, MBBS, PhD, FRACP, FRCPA, Michael E. Buckland, MB, BS, PhD, FRCPA, Ruta Gupta, MD, FRCPA, Michael Gonzales, MB, BS, FRCPA, G. Michael Halmagyi, MD, FRACP

Abstract: We describe 2 patients with inexorably progressive pseudotumor syndrome (intracranial hypertension without mass lesion or ventriculomegaly) both initially misdiagnosed as having idiopathic intracranial hypertension and who were eventually found to have spinal leptomeningeal lymphoma. Neither had, at any time, any clinical signs of a spinal cord or root lesion. We discuss the possible implications of these observations regarding the diagnosis and mechanism of the pseudotumor syndrome.

Journal of Neuro-Ophthalmology 2013;33:13–16
doi: 10.1097/WNO.0b013e31823ff460

Pseudotumor syndrome is the term used for cases of intracranial hypertension without mass lesion or ventriculomegaly (1). It is often idiopathic (2), in which case the term “pseudotumor cerebri” is also used (3), but in fact it has many possible causes (1). Rarely, pseudotumor syndrome can be due to intrinsic or extrinsic spinal tumors (4–7), chronic inflammatory (8) or acute demyelinating (9) polyneuropathies, and cryptococcal (10), leukemic (11), carcinomatous (12), gliomatous (13), or lymphomatous (14–16) cranial meningitis.

We describe 2 patients who presented with the pseudotumor syndrome and were eventually found to have spinal leptomeningeal lymphoma (i.e., lymphomatous spinal meningitis). Neither had any evidence of a spinal cord or root lesion throughout their clinical course, and good-quality MRI of the brain and spine initially showed no leptomeningeal enhancement. We discuss the possible implications of these observations regarding the diagnosis and pathophysiology of the pseudotumor syndrome.

CASE 1

A 43-year-old immunocompetent woman presented with a 12-month history of headache, dizziness, and transient visual obscurations. Visual acuity was 20/20 in each eye; visual fields showed bilaterally enlarged blind spots without peripheral constriction, and there was bilateral papilledema. Brain and spine MRI with gadolinium was normal. Lumbar puncture showed an opening pressure of 27 cm H2O with cerebrospinal fluid (CSF) protein of 4.3 g/L (normal, <0.4 g/L) and glucose of 0.8 mmol/L (normal, >2.5 mmol/L) and no cells.

Despite elevated CSF protein, the patient was treated for idiopathic intracranial hypertension (IIH) with repeated lumbar punctures (4 in total). Opening pressures ranged from 27 to 34 cm H2O. The CSF protein stayed high, and the glucose stayed low. Flow cytometry was performed each time, and no atypical lymphocytes or malignant cells were detected.

Two months later, the patient was transferred to our care. Repeat spine MRI now showed meningeal enhancement around lumbar nerve roots, upper thoracic cord, and the cerebellum. CSF revealed abundant, large, atypical lymphocytes, suggestive of lymphoma, but the diagnosis could not be confirmed on flow cytometry or bone marrow biopsy. Biopsy of a lumbar nerve root and sheath showed involvement by an extranodal T-cell lymphoma, characterized by sheets of large atypical CD3+ T lymphocytes (Fig. 1). Despite chemotherapy, the patient died 4 months after diagnosis.
CASE 2
A 49-year-old man was evaluated elsewhere with 6 weeks of headache and visual obscurations and was found to have bilateral papilledema. Visual acuity was 20/20 in each eye with enlarged blind spots but intact peripheral fields. Contrast-enhanced brain MRI showed bilateral dilation of the optic nerve sheaths, normal ventricular size, no mass lesions, and no meningeal enhancement. Magnetic resonance venogram revealed an irregular superior sagittal sinus, a hypoplastic left transverse sinus, and intrinsic stenosis of the right transverse sinus. He was felt to have IIH, although a lumbar puncture was not performed. Acetazolamide was commenced but the papilledema worsened with the development of peripheral visual field constriction.

Two months later, cerebral venography and manometry showed venous hypertension and stenoses in the posterior sagittal and right transverse sinus (superior sagittal sinus pressure of 47 mm Hg and pressure gradient across stenosis of 18 mm Hg). The stenoses were stented, with immediate resolution in venous hypertension and pressure gradient. Visual obscurations improved, but the papilledema did not.

Fifteen months later, vision was 20/60 in the right eye and 20/20 in the left eye. Lumbar puncture was now performed and showed an opening pressure of 30 cm H₂O, a CSF protein of 4.22 g/L and glucose of 0.2 mmol/L, 45 white cells/mm³ (90% lymphocytes and 10% monocytes). Flow cytometry revealed an increased percentage of CD19, CD10, and CD19⁺ B cells but was not diagnostic of lymphoma. Viral and bacterial cultures were negative, as was polymerase chain reaction for cryptococcal and tuberculosis. Brain and spine MRI showed leptomeningeal enhancement extending from the conus to the cerebellum and involving the roots of the cauda equina (Fig. 2). Positron emission tomographic scan showed diffuse fluorodeoxyglucose (FDG) uptake overlying the cervical cord and cauda equina, raising suspicion of leptomeningeal lymphoma. Four more lumbar punctures (the patient underwent a total of 6) and a bone marrow biopsy all failed to confirm lymphoma.

Because the patient’s vision continued to deteriorate and his intracranial pressure remained high, a Rickham reservoir and a ventriculoperitoneal shunt were inserted. Ventricular CSF samples taken from the reservoir showed a normal protein (0.36 g/L), glucose (2.6 mmol/L), and 5 white cells/mm³. The dura, leptomeninges, and cerebral cortex were biopsied during placement of the Rickham reservoir. In addition, laminectomy was performed with biopsy of a sacral nerve root and its sheath. Biopsies at both sites showed leptomeningeal tissue with a heavy mixed lymphoplasmacytic infiltrate, including scattered atypical intermediate- to 40x40

FIG. 1. Case 1. A. Biopsy of lumbar nerve root reveals clusters of atypical large lymphocytes (hematoxylin & eosin, ×40). B. With immunostain, these cells are CD3⁺ (×63).


Original Contribution

Copyright © North American Neuro-Ophthalmology Society. Unauthorized reproduction of this article is prohibited.
large-sized CD20+ B cells. These atypical B cells focally accumulated along the Virchow–Robin spaces in the superficial cortex (Fig. 3). They were immunonegative for CD10, CD5, cyclinD1, MUM-1, CD23, and bcl-6 as well as for EBER-1 in situ hybridization. The morphology and immunophenotype were highly suspicious for a large B-cell non-Hodgkin lymphoma.

The patient was given “R-MVBP” chemotherapy (rituximab, methotrexate, lomustine, etoposide, and prednisolone). His hearing returned to baseline; vision remains counting fingers in the right eye and 20/80 in the left eye. The leptomeningeal enhancement resolved (Fig. 4), and repeat lumbar CSF showed a protein of 1.36 g/L, glucose of 3.0 mmol/L, 2 white cells/mm³, and 143 red cells/mm³.

DISCUSSION

In both our cases, spinal leptomeningeal lymphoma caused an inexorably progressive pseudotumor syndrome without any clinical signs of a spinal cord or nerve root lesion and initially no imaging evidence of meningeal disease. One clue to the correct diagnosis was the CSF characterized by high protein, very low glucose, and atypical lymphocytes. However, in our cases, CSF analysis was insufficient to establish the diagnosis. Contrast-enhanced MRI of the spine eventually showed leptomeningeal and cauda equina nerve root involvement and lead to leptomeningeal biopsy.

In the 3 previous reports of leptomeningeal lymphoma causing pseudotumor syndrome (14–16), only the cranial meninges were reported to be involved, but the spinal meninges were not examined. In 2 reports, the diagnosis was eventually made on CSF studies (14,15) and in the third at autopsy (16). In 2 reports (14,15), brain MRI showed no meningeal enhancement, although the spine was not imaged.

Spinal leptomeningeal lymphoma is very rare, especially in immunocompetent patients. All 3 cases (17–19) reported in the literature presented with symptoms of radiculopathy and were difficult to diagnose. Spinal MRI showing nerve root thickening was found in all 3 cases, leading to biopsy in 2 cases (17,18), and in the other case, diagnosis was confirmed on CSF analysis (19).

Solid spinal tumors, especially thoracolumbar (4,20), can cause either communicating hydrocephalus (6) or pseudotumor syndrome (4,5,7). Why intracranial hypertension develops with spinal tumors and why the ventricles do or do not enlarge is not understood. Proposed mechanisms for intracranial hypertension include mechanical obstruction (6), increased CSF protein “clogging” absorption pathways (6,7), meningeal inflammation or invasion of the meninges, tumor-secreted products causing arachnoiditis (6), or changes in craniospinal compliance by the tumor disrupting the lumbosacral CSF reservoir (5–7). The assumption that high protein produced by the spinal tumor blocks absorption at the arachnoid villi causing pseudotumor syndrome is open to debate since CSF protein concentration rostral to the tumor is usually only one tenth of that caudal to the tumor (6).

This report of nonsolid spinal tumors causing intracranial hypertension appears unique. We propose that in our 2 patients, involvement of the lumbosacral nerve roots by lymphoma or the grossly elevated spinal CSF protein might have blocked CSF absorption at the spinal level. CSF is absorbed by the spinal nerve roots as well as by the arachnoid villi and olfactory bulbs (21). When cranial CSF absorption is blocked in animals, there is compensatory clearance along the lumbosacral roots (22). It has been estimated

FIG. 3. Case 2. A. Brain biopsy shows atypical intermediate to large lymphocytes, extending down from the leptomeninges into the Virchow–Robin spaces (hematoxylin & eosin, ×63). B. Lymphocytes are diffusely CD20+ with immunostaining (×63).

FIG. 4. Contrast-enhanced sagittal T1 spine MRI shows resolution of leptomeningeal enhancement.
that 38% ± 20% (mean ± SD) of CSF absorption in resting healthy individuals and 76% ± 25% (mean ± SD) in active individuals is from the spinal subarachnoid space (23).

Pseudotumor syndrome in chronic inflammatory (8) and acute demyelination (9) polyneuropathies might also be due to abnormal spinal CSF reabsorption and not simply due to raised CSF protein, which is not present in all cases (9). In these neuropathies, there is swelling of the lumbosacral nerve roots (24,25), suggesting a possible site of decreased CSF reabsorption. Pseudotumor syndrome also occurs after blood patching of CSF leaks (26), possibly also by decreasing spinal CSF reabsorption.

Our patients demonstrate that spinal leptomeningeal disease may cause pseudotumor syndrome with no clinical evidence of spinal disease. CSF examination may reveal elevated protein and lowered glucose; atypical cells may only appear late in the disease. In both cases, the examination was eventually made after MRI of the spine showed leptomeningeal enhancement. This emphasizes the importance of ordering contrast-enhanced spinal MRI in patients with atypical pseudotumor syndrome.

REFERENCES


