CASE REPORT

Diffuse large B-cell lymphoma of the cauda equina

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SUMMARY

Primary central nervous system (CNS) lymphoma is a rare form of non-Hodgkin's lymphoma. The clinical presentation is variable, depending on its localisation within the nervous system. Only 1% of primary CNS lymphoma emerges in the spinal cord, and the prevalence of primary lymphoma of the cauda equina is unknown, but probably even rarer. Diagnosing primary lymphoma of the cauda equina is difficult, since it can mimic other more common disorders such as a herniated disc, especially in its early stages. Here we present two cases of primary cauda equina lymphoma in which diagnostic work up took a long time, as the final diagnosis was only reached after a nerve root biopsy.

BACKGROUND

In both cases we suspected a leptomeningeal malignancy, but many repeated analyses of the cerebrospinal fluid did not yield any malignant cells. As a consequence, an extensive period of time elapsed until a final diagnosis could be made by a nerve root biopsy. By presenting these cases we hope to make clinicians more aware of the possibility of repeated negative cerebrospinal fluid test results in this disorder, so a biopsy should be performed earlier to diagnose this essentially treatable cancer. We also encourage the use of an intraoperative smear to avoid extensive surgery.

CASE PRESENTATION

Case 1

A 75-year-old previously healthy woman presented with weakness of her left foot extensors (Medical Research Council (MRC) grade 4/5) with numbness and pain in the left L5 dermatome. MRI showed a small L4–L5 disc herniation and because of the paresis she underwent a lumbar laminectomy. However, her symptoms did not subside and over the next months the paresis expanded to her upper left leg (MRC 3/5). In addition, atrophy and light paresis developed in her right leg (MRC 4/5) and her right upper arm (MRC 4/5). Reflexes in her legs were absent and a polyradiculopathy was considered.

Case 2

A 71-year-old previously healthy woman presented with paraesthesiae and radiating pain in her right leg, compatible with a radiculopathy S1. However, a lumbosacral MRI showed no abnormalities. She was referred to an anaesthesiologist for multiple transforaminal injections, with varying pain relief. During the following year she gradually developed a progressive paresis of her right and left foot extensors and ultimately also of the proximal leg muscles. One and a half years after the start of her symptoms she had become

bedridden. Neurological examination at that point showed a paralysis of the distal lower extremities (MRC 0/5) and a severe paresis of the proximal muscles of her right (MRC 3/5) and left legs (MRC 1/5); an areflexia and atrophy of the m. quadriceps were also present; all of which were suggestive of a lumbosacral polyradiculopathy.

INVESTIGATIONS

Case 1

- ▶ *Routine haematology and biochemistry*: Within normal limits, HIV serology was negative.
- ▶ *Cerebrospinal fluid (CSF) analysis (four times)*: Leucocytes up to 140/μL with elevated protein (3.57 g/L, ref 0.26–0.79 g/L) but normal glucose (2.9 mmol/L). Four cytology and fluorescence-activated cell sorting analyses (FACS) showed atypical cells, but no malignant cells. One sample showed IgM antibodies against *Borrelia burgdorferi* but the subsequently sample showed no antibodies. In addition, PCR and immunoblot on *B. burgdorferi* were also negative.
- ▶ *Electromyography (EMG; twice)*: Diffuse signs of denervation of nerve L5, S1 and C6 compatible with a polyradiculopathy.
- ▶ *Lumbosacral MRI (three times)*: Thickening of the cauda equina nerve roots with contrast enhancement (figure 1).
- ▶ *Nerve biopsy of the left L5-root*: Endoneural and perineural small lymphocytes and large, atypical cells with little cytoplasm and large polymorphic nuclei and a leucemic growth pattern. The larger cells were positive for CD20 and also BCL 6, and the MIB-1 showed a vastly increased proliferation index, compatible with the diagnosis of large diffuse B-cell lymphoma (figure 2).

Case 2

- ▶ *Routine haematology and biochemistry*: Within normal limits, HIV serology was negative.
- ▶ *CSF analysis (three times)*: Leucocytes up to 67/μL with strongly elevated protein 10.42 g/L (0.26–0.79 g/L) and low glucose <0.6 mmol/L. Three cytology and two FACS analyses showed atypical, but no malignant cells. All tests for infectious agents were negative.
- ▶ *EMG (twice)*: Progressive signs of denervation in roots L4, L5, S1 and S2, compatible with a lumbosacral polyradiculopathy.
- ▶ *Lumbosacral MRI (three times)*: Thickening and enhancement of multiple lumbosacral nerves (figure 3).
- ▶ *Positron emission tomography (PET)-CT*: Increased fluorodeoxyglucose-load at the lumbosacral nerve roots. No other abnormalities (figure 4).

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Figure 1 Upper part showing a sagittal (left) and transversal (right) T2-weighted MRI image of the lumbosacral region of the patient in case 1, without extreme thickening of the nerves. The lower part shows the T1-weighted image after intravenous gadolinium with clear enhancement of the cauda equina.

► *Nerve biopsy of right L5-root*: Atypical cells with increased polymorphic nuclei and a decreased amount of surrounding cytoplasm. Presence of apoptosis. The atypical cells were

positive for CD20, CD79 and BCL-6 staining and the MIB-1 was strongly increased, compatible with the diagnosis of a large diffuse B-cell lymphoma ([figure 5](#)).

Figure 2 Upper part displays H&E low-power magnification (left) and H&E high-power magnification (right) showing nerve infiltration with medium to large tumour cells with little cytoplasm, large nuclei and prominent nucleoli. Lower part showing immunohistochemistry positive for CD20, suggesting B-cell origin of the tumour cells.

Figure 3 MRI of the lumbosacral region in case 2. There is also extreme thickening of the nerves with clear enhancement after intravenous gadolinium.

DIFFERENTIAL DIAGNOSIS

In both cases a final diagnosis of a primary CNS, large diffuse B-cell lymphoma was made.

However, both patients first presented with a single radiculopathy, mimicking a disc herniation. When the disorder progressed and examination showed weakness with absent reflexes and atrophy, polyradiculopathy was considered and confirmed with EMG. The differential diagnosis of a polyradiculopathy is extensive, including malignant, infectious and other inflammatory (eg, autoimmune) causes.

Figure 4 Positron emission tomography (lower part) and corresponding CT image (upper part) of the patient in case 2. Note the increased fluorodeoxyglucose load at the lumbosacral nerve roots.

The MRI displayed thickened nerve roots with contrast enhancement, suggesting also an infective, inflammatory or intradural neoplastic process. The CSF showed a pleocytosis with strongly elevated protein level. The strong elevated protein was especially suggestive of a malignancy. No infectious agents, besides the false-positive *Borrelia* test, were found in the CSF, which made an infectious cause unlikely. A nerve root biopsy eventually led to the final diagnosis of a lymphoma.

TREATMENT

Case 1

The patient received 4 weeks of intravenous ceftriaxone for a putative diagnosis of neuroborreliosis. At the time of the definitive diagnosis of primary CNS lymphoma the patient had deteriorated to a point where she was no longer considered to be eligible for chemotherapy or radiotherapy. Oral dexamethasone 4 mg twice daily was initiated and she was transferred to a nursing home.

Case 2

The patient was referred to the haemato-oncologist and started with intravenous chemotherapy (doxorubicine, vincristine, cyclofosamide, prednisone and rituximab; R-CHOP). In total she received eight cycles. In addition, she received 10 intrathecal injections of methotrexate.

OUTCOME AND FOLLOW-UP

Case 1

In the following 6 months the patient deteriorated further. The lymphoma progressed and paresis of her legs and arms worsened. In the end, the cranial nerves were also invaded and she developed dysphagia, dysarthria and loss of vision. Six months after discharge and 10 months after onset of symptoms she passed away.

Figure 5 Case 2, H&E magnification also showing nerve infiltration with tumour cells with little cytoplasm. Lower part showing immunohistochemistry positive for CD-20, suggesting B-cell origin of the tumour cells.

Case 2

After three cycles of R-CHOP evaluation showed a good response in the patient. Therefore, it was decided to continue systemic chemotherapy and no radiotherapy was given. Evaluation after eight cycles of chemotherapy showed a complete response. Presently her motor function in the left leg has improved a little, but the right leg remains non-functional. She currently participates in a rehabilitation programme and is frequently checked by her haematologist.

DISCUSSION

Primary Non-Hodgkin's lymphoma (NHL) of the CNS is uncommon and generally affects the brain.^{1 2} Large diffuse B-cell lymphoma is the most common form of CNS NHL. Direct infiltration of the cauda equina is rare and can be the result of a primary localised, disseminated or recurrent NHL. In a large study of 150 cauda equina tumours the incidence of lymphomas was 1.3%³ and over the years only a few case reports of primary cauda equina lymphoma have been published.^{2 4 5} Examination of the spine with MRI and intravenous gadolinium is recommended and cytomorphological examination of the CSF with immunophenotyping may give the final diagnosis of lymphoma.⁴ However, others⁶ have also reported repeated inconclusive cytological examinations, where a final diagnosis could only be made after a nerve root biopsy.

In the first patient 5 months elapsed between first visit to the neurologist and the final diagnosis. Patient two was referred to our hospital for a second opinion 10 months after her first visit to a neurologist and a final diagnosis was made 5 months later.

There is an understandable reluctance to do a nerve root biopsy for fear of irreversible nerve damage. There is not much literature on this, but the few papers on the subject suggest that complication rates are low.^{7 8} As primary CNS lymphoma is a potentially curable cancer,⁹ a nerve root biopsy should be

performed earlier in the work up, for example, after two negative CSF examinations. When biopsy is conducted an intraoperative smear can help to determine the extent of surgery, especially since the differential diagnoses include other intradural tumours such as ependymomas, neurofibromas or schwannomas. With an early diagnosis of lymphoma, extensive, unnecessary surgery can be avoided.² In addition, treatment with glucocorticoids leads to clinical improvement in neoplasms, inflammatory processes and lymphomas; however, it can also obscure the diagnosis of lymphoma on biopsy, so an early biopsy is recommended.

Learning points

- Complex cases should be discussed by a neuro-oncology multidisciplinary team and neurosurgical consultation sought early on.
- Central nervous system (CNS) lymphoma should be considered in the differential diagnosis of intradural lesions affecting the cauda equina.
- Cytomorphological examination with immunophenotyping of cerebrospinal fluid is a valuable diagnostic tool in detecting lymphoma, but can be repeatedly inconclusive.
- Fear of causing permanent nerve damage is not justified for delaying the cauda equina biopsy.
- Early diagnostic biopsy and intraoperative smear helps in initiating the right treatment and avoids unnecessary, extensive surgery.

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