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Case Report

Essentials for early diagnosis of primary intramedullary spinal cord lymphoma. How to suspect primary intramedullary spinal cord lymphoma early and proceed to invasive biopsy? A case report and literature review

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ABSTRACT

Background: Primary intramedullary spinal cord lymphoma (PISCL) is an extremely rare condition. Early diagnosis is very difficult due to the nonspecific clinical and imaging findings. A biopsy is essential for a definitive diagnosis, but courage is required to perform the surgery. Here, we present a case of PISCL and suggest useful indicators for accurate diagnosis of this pathological entity.

Case Description: A 70-year-old woman presented with subacute bilateral lower-limb paralysis, disturbance of warm and pain sensations, and vesicorectal disturbance. Magnetic resonance imaging showed a contrast-enhanced mass from C7 to Th2 and large, edematous lesions from the upper cervical to lower thoracic spinal cord. Elevated uptake of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) was identified in the enhanced regions on FDG-positron emission tomography (PET). Cerebrospinal fluid (CSF) analysis revealed highly elevated levels of β2-microglobulin (β2-MG). Steroid pulse therapy and therapeutic plasma exchange were performed for suspected myelitis, but symptoms did not improve. Spinal cord biopsy was, therefore, performed for treatment-resistant myelopathy. Histopathological examination revealed diffuse large B-cell lymphoma, which was diagnosed as PISCL because systemic examination showed no other findings suggestive of malignant lymphoma.

Conclusion: In cases with poor response to treatment and a progressive course, PISCL should be considered, and spinal cord biopsy should be performed if PET shows increased ^{18}F-FDG uptake and β2-MG is elevated in CSF.

Keywords: Accurate diagnosis, Positron emission tomography, Primary intramedullary spinal cord lymphoma, Surgical biopsy, β2-microglobulin

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is rare, accounting for <1% of all lymphomas. It is confined to the eye, brain, leptomeninges, and spinal cord, with no systemic

involvement.[3,6] On the other hand, primary intramedullary spinal cord lymphoma (PISCL) is extremely rare, accounting for <1.0% of all malignant lymphomas that occur in the central nervous system (CNS).[10,11] The majority of patients present in their 50s, affecting primarily the chest and neck, with low long-term survival rates and high mortality rates.[3] This pathology is associated with rapidly progressive spinal cord symptoms, so differentiation from various inflammatory diseases such as neuromyelitis optica spectrum disorders (NMOSDs) and neoplastic diseases such as malignant gliomas must be made as soon as possible. However, the low positive rate of cytology in cerebrospinal fluid (CSF) necessitates surgical biopsy for early and accurate diagnosis.[1,3,4,7,10] Here, we present a case of PISCL in which the diagnosis was confirmed by surgical biopsy, and we suggest useful indicators for the accurate diagnosis of this entity. Both ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) and levels of β2-microglobulin (β2-MG) in CSF appear very useful for rapid and accurate diagnosis, enabling early therapeutic intervention.

CASE DESCRIPTION

General remarks

A 70-year-old woman presented with a 4-month history of numbness in the left chest that had gradually worsened and then spread to both lower extremities with associated gait disturbance. She was, therefore, admitted to our hospital. She had no obvious history of trauma, systemic diseases, or metabolic disorders. Neurological examination on admission revealed dysesthesia, decreased warm and pain sensations in the thoracic (Th)4 vertebral region and lower and hyperreflexia in both lower limbs. Complete paralysis and pronounced numbness were apparent in both lower limbs. Magnetic resonance imaging (MRI) showed a longitudinally spreading, intradural spinal cord lesion in the cervical (C)7–Th2 region, with gadolinium (Gd) enhancement on T1-weighted imaging (WI) with diffuse swelling within the C2–Th6 levels [Figure 1]. No other lesions were identified within the spinal cord or intracerebral region. Markedly high ^{18}F-FDG uptake was seen on ^{18}F-FDG-PET within the enhanced region (tumor-to-contralateral normal brain tissue ratio [TNR]: 2.52) [Figure 2], with no obvious ^{18}F-FDG accumulation in the brain or other organs. CSF analysis revealed a slightly elevated lymphocytic cell count (11/μL) and highly elevated β2-MG (4.2 mg/L).

Progress of treatment

Transverse myelitis was initially suspected, and steroid pulse therapy and simple plasma exchange therapy were performed, but no symptom improvement was obtained. Therefore, to confirm the histological diagnosis and plan effective treatment for the primary disease, a surgical biopsy of the lesion was performed under a posterior approach (total Th1–Th3 laminectomy). The dura mater was incised to identify the spinal cord; then, gentle blunt dissection of the posterior median sulcus was performed to locate the lesion. The lesion did not show an obvious macroscopic margin, but abnormal tissue was easily removed for biopsy [Figure 3a]. Histological examination with hematoxylin and eosin staining revealed glial tissue with diffuse infiltration of atypical medium-to-large lymphocytes with irregular nuclei and prominent nucleoli in the edematous tissue. Immunohistochemical examination demonstrated a positive result for cluster of differentiation (CD)20 and a negative result for CD3, suggesting a B lymphohematopoietic system tumor, and the histological diagnosis was diffuse large B-cell lymphoma [Figures 3b-d]. In addition, a non-germinal center B-cell -like phenotype was identified from the results of CD10(−), bcl-6(+), and MUM1(+) according to the decision tree proposed by Hans *et al*.[5] Since no evidence suggested malignant lymphoma in the CNS, including the eyes other than the spinal cord, and FDG-PET of the thorax and abdomen showed no systemic lymph node enlargement, PISCL was diagnosed.

Postoperative course

The patient was placed on rituximab, methotrexate, procarbazine, and vincristine (R-MPV regimen). He was administered a total of four cycles, but serial MRI during the care process did not show any tumor shrinkage effect, so local radiation therapy was performed (40 Gy in 20 fractions). The subsequent course was uneventful, with MRI and ^{18}F-FDG-PET at ten months after completion of chemoradiotherapy, showing a complete disappearance of Gd and ^{18}F-FDG accumulation in the spinal cord [Figure 4]. The patient was judged to have achieved complete metabolic remission. The ethics committee of our institution approved the clinical study of this case, and informed consent was obtained from the patient.

DISCUSSION

Malignant lymphoma arising in the CNS, as so-called PCNSL, is a rare form of extranodal non-Hodgkin lymphoma. The clinical characteristics of PISCL patients obtained from the literature review are shown in Table 1.[3] The PISCL subtype is an extremely rare pathology, accounting for <1.0% of PCNSLs.[1,3,4,7,10] Clinically, the disease is associated with progressive spinal cord symptoms and large spinal cord lesions on neuroimaging, and neuroimaging findings mimic other progressive neurological disorders such as other CNS tumors (e.g., malignant gliomas), demyelinating disease, autoimmune conditions, CNS infections, and various inflammatory lesions such as NMOSD.[7,11] MRI is

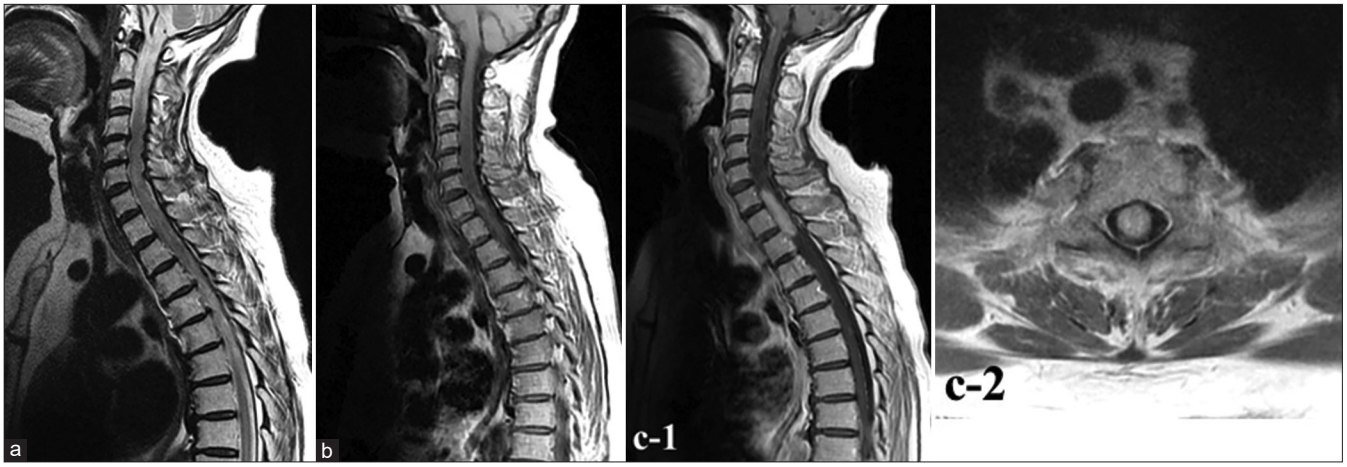

Figure 1: Results of magnetic resonance imaging (MRI) on admission. MRI shows an intradural, longitudinally spreading spinal cord lesion in the cervical (C)7 to thoracic (Th)2 region, with gadolinium enhancement on T1-weighted imaging (WI) and diffuse swelling from the C2 to Th6 level. (a) Sagittal T2-weighted imaging. (b) Sagittal T1-weighted imaging (T1-WI) with non-contrast sequence. (c-1) Sagittal gadolinium-enhanced T1-WI. (c-2) Axial Gd-enhanced T1-WI.

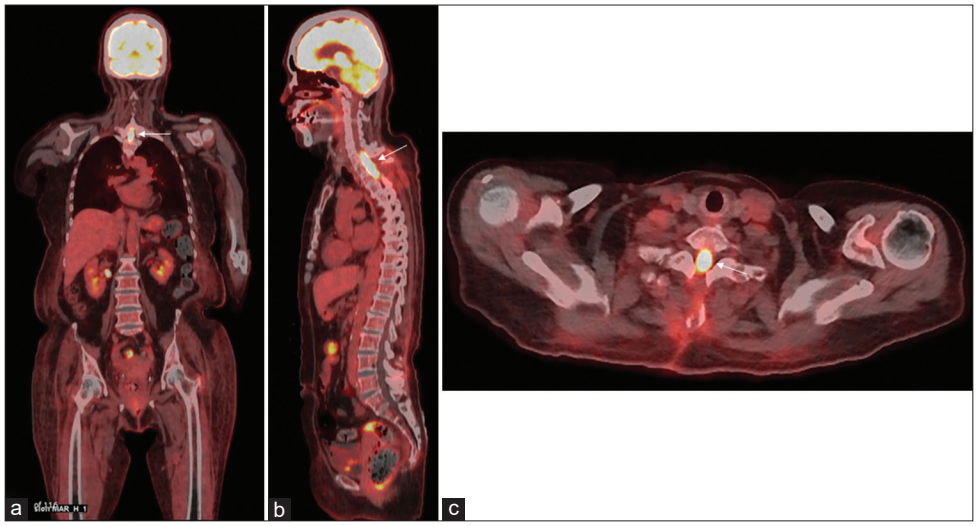

Figure 2: Preoperative ^{18}F-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography reveals markedly elevated uptake of FDG (white arrow) in the spinal cord (cervical7– thoracic2). (a) Coronal view. (b) Sagittal view. (c) Axial view.

the clinically preferred imaging modality for diagnosing PISCL. Typically, PISCL presents as a hyperintense lesion on T2-weighted imaging (T2-WI)[8] with homogenous enhancement on Gd T1-weighted imaging.[7,12] However, these features are also seen with malignant gliomas, metastatic tumors, and neurosarcoidosis.[7] An invasive spinal biopsy is, therefore, necessary for accurate diagnosis.[1,3,7,11] Because the disease often responds to steroids in the early stages, clinicians are often hesitant to perform a biopsy, thus delaying diagnosis and treatment.[1,3,7,11] As reported by Hachicha *et al*., the diagnosis previously took an average of approximately 16 months from symptom onset.[4] Therefore, early and rapid diagnosis timely and appropriate treatment of PISCL are extremely crucial in improving the survival of the patients. In the present case, as in previous reports, the patient was initially treated with steroid pulse therapy and plasma exchange with inflammatory disease in mind. Symptoms were initially relieved but later relapsed early, leading to diagnosis from spinal cord biopsy three months after onset. The challenge is thus how to suspect PISCL and make an early decision to perform an invasive spinal cord biopsy.

To date, no consensus has been reached on appropriate presurgical diagnostic evaluations. We consider that key points in the diagnosis of PISCL are imaging findings from ^{18}F-FDG-PET and CSF.[6] PET is widely used as a

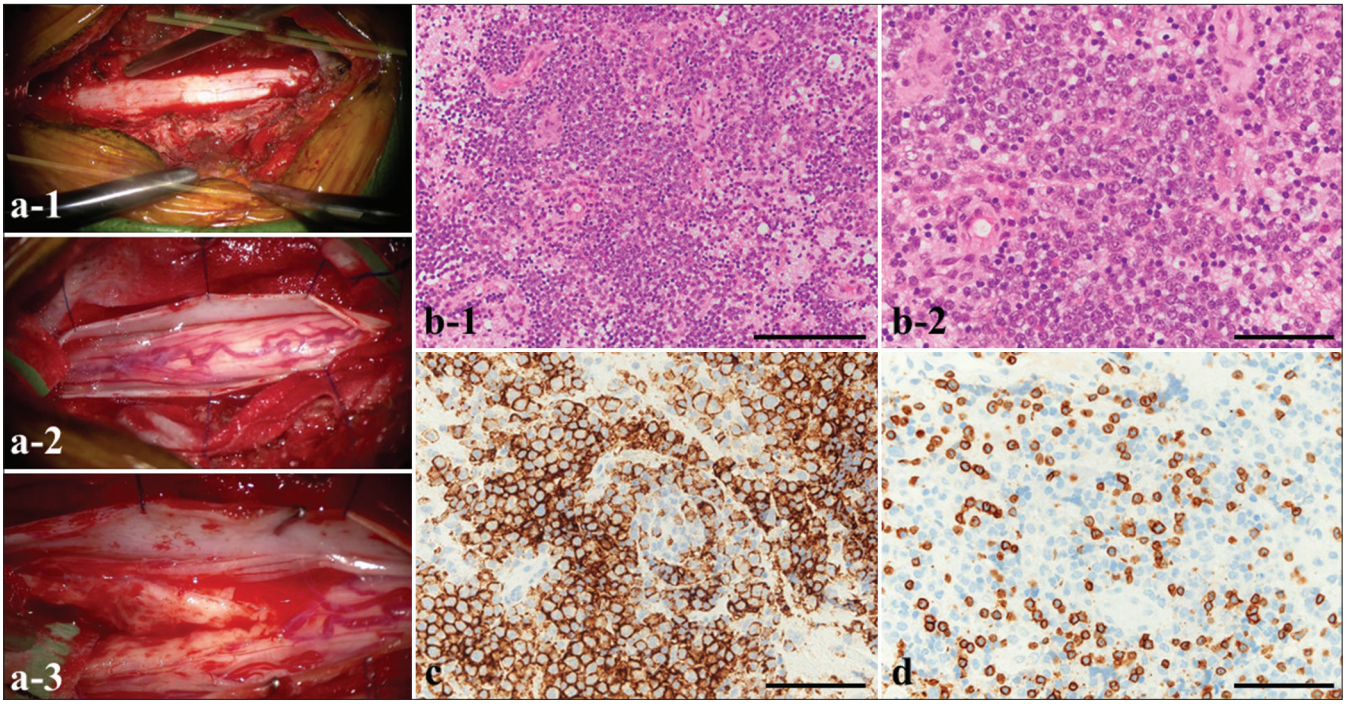

Figure 3: (a) Intraoperative photographs. (a-1) Total laminectomy (Th1–3). (a-2) The dura mater is incised to identify the spinal cord. (a-3) Gentle, blunt dissection of the posterior median sulcus is performed to locate the lesion, which does not show an obvious macroscopic margin. (b) Histopathology of the resected tumor (b-1 and b-2) shows that large, atypical lymphocytes have extensively infiltrated the lesions. (c) The cells reveal positive staining for a cluster of differentiation (CD) 20 (d) and negative staining for CD3. Magnifications: (b-1) ×100; (b-2, c, d) ×400. Scale bars: (b-1) 400 μm; (b-2, c, d) 100 μm.

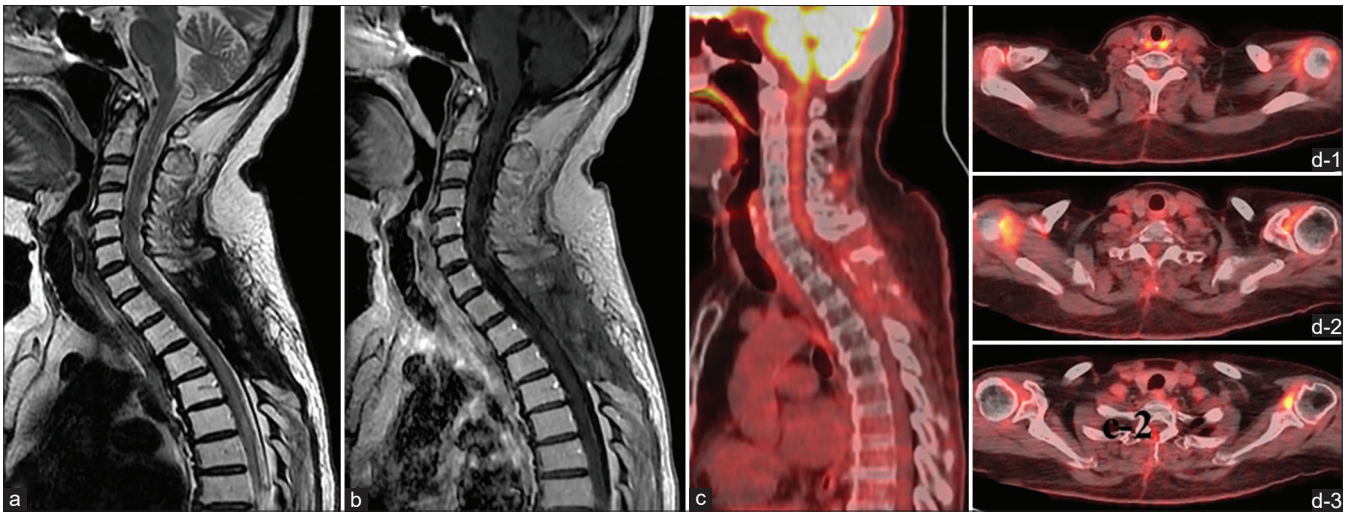

Figure 4: (a) Sagittal T2-WI, (b) Gd-enhanced MRI and (c: coronal view; d-1,d-2,d-3: axial view) ^{18}F-FDG-PET at 10 months after chemoradiotherapy show no residual tumor.

functional imaging modality applying radiotracers such as ^{11}C-Methionine and ^{18}F-FDG.[14] We have previously reported that the TNR of 2.4 from ^{18}F-FDG-PET was consistent with the pathological diagnosis of PCNSL, with this method offering 83.8% sensitivity and 95.2% specificity.[6] Conversely, the TNR from met-PET was very high for PCNSL but not significantly different from that for glioblastoma (GBM).[6] These results suggested ^{18}F-FDG-PET analysis as a useful imaging modality for preoperative differentiation of PCNSL from GBM.

Regarding CSF findings, past reports have stated that C-X-C motif chemokine ligand 13 (CXCL13), interleukin (IL)-10,

Table 1: Literature review: Clinical characteristics of primary intramedullary spinal cord lymphoma.

Parameter	Value
No. of patients	33
Female gender (%)	20 (60.6)
Age (50 years)	19 (57.6)
Tumor site (%)	
Cervical	18 (62.1)
Thoracic	20 (69.0)
Lumbar	8 (27.6)
Sacral	3 (10.3)
Extramedullary involvement	12 (41.4)
Treatment (%)	
Surgery, chemotherapy and radiation	4 (19.0)
Surgery and chemotherapy	1 (4.8)
Surgery and radiation	2 (9.5)
Chemotherapy and radiation	10 (47.6)
Chemotherapy	2 (9.5)
Radiation	1 (4.8)
Surgery	1 (4.8)

No.: Number

soluble IL-2 receptor (sIL-2R), and β2-MG in CSF show excellent diagnostic ability as biomarkers for PCNSL.[3,6,9] However, since CXCL13 and IL-10 are difficult to measure in most facilities and the tests are not versatile, we focused on measuring β2-MG in CSF.[6] Previous reports have demonstrated that a concentration of β2-MG ≥2.0 mg/dL in CSF provided 95.0% sensitivity and 85.7% specificity for differentiating PCNSL from GBM.[6] In our present case, the TNR on ^{18}F-FDG-PET was 2.52, and β2-MG in CSF was 4.2 mg/L, meeting the above criteria. Whether what is true regarding PCNSL also applies to PISCL remains unclear, but in cases of unexplained progressive spinal cord lesions, surgical biopsy may be warranted if these findings are present.

Finally, few reports have dealt with the treatment of PISCL, and, at this point, no definitive methods have been identified. Surgery, radiation therapy, and chemotherapy are commonly used for PISCL, alone or in combination.[1,3,4,7,10] Previous reports have most commonly used the combination of radiation therapy and chemotherapy, accounting for exactly half of all treatments [Table 1].[3] With regard to long-term efficacy, chemotherapy alone appears more beneficial than other treatment modalities, but detailed reports on that regimen remain lacking.[3,13] On the other hand, the dose of radiotherapy is related to effectiveness, with doses <40 Gy associated with a high risk of poor therapeutic response and recurrence.[2] In the present case, four cycles of chemotherapy with the R-MPV regimen and radiation therapy (40 Gy) were added, and the patient remained recurrence-free for at least ten months after treatment.

Several limitations to this report must be kept in mind. As PISCL is a rare neurological condition, few cases have been reported. Further, research, accumulation of more cases, and longer follow-up of patients are required to obtain a better understanding of the pathological conditions and appropriate therapies associated with PISCL.

CONCLUSION

We have reported an extremely rare case of PISCL, diagnosed and confirmed by early surgical biopsy and treated with chemoradiotherapy using the R-MPV regimen. In cases showing progressive spinal cord lesions of unknown cause, PISCL should be considered as a differential diagnosis. In particular, if MRI shows a uniform contrast effect and extensive edema is seen on T2-WI/MRI, β2-MG levels in CSF should be measured, and ^{18}F-FDG-PET and early surgical biopsy performed to investigate the possibility of PISCL. The successful clinical management in this case provides an important potential option for treating PISCL patients.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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