Lymphomatosis Cerebri with Intramedullary Spinal Cord Involvement

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Abstract

Lymphomatosis cerebri (LC) is a rare form of primary central nervous system lymphoma (PCNSL). Little is known about cases of LC with spinal cord involvement. Among the 11 PCNSL patients treated in our hospital during a four-year period, we identified two cases of LC with spinal cord lesions. One showed a spinal cord lesion followed by leukoencephalopathy. The other showed a spinal cord lesion after LC. In both cases, the histopathology was diffuse large B-cell lymphoma. It is possible that LC may affect the entire central nerve system, and tumor infiltration to the brain and spinal cord in LC may occur more frequently than has been previously considered.

Key words: diffuse large B cell lymphoma, intramedullary spinal cord tumor, leukoencephalopathy, lymphomatosis cerebri, magnetic resonance imaging, primary central nervous system lymphoma


Introduction

Primary central nervous system lymphoma (PCNSL) is a rare variant of extranodal non-Hodgkin’s lymphoma that is confined to the eyes, brain, leptomeninges and spinal cord. The most common radiological finding of PCNSL in immunocompetent patients is a single lesion or multiple focal lesions with homogeneous contrast enhancement (1-3). Lymphomatosis cerebri (LC) is an exceedingly rare variant of PCNSL characterized by the diffuse infiltration of lymphoma cells, and its presentation on magnetic resonance imaging (MRI) shows diffuse leukoencephalopathy with only mild or absent contrast enhancement (4, 5). LC is associated with no specific MRI features; therefore, physicians sometimes fail to distinguish LC from other causes of leukoencephalopathy. In addition, intramedullary spinal cord lymphoma is extremely rare (6, 7), and little is known about the clinical features of LC accompanied by intramedullary spinal cord involvement. The histopathological findings of several autopsied cases of PCNSL showed a widespread appearance with spinal cord involvement (8). Although the pathological findings of these autopsied cases suggest that spinal cord involvement is occasionally found in patients with PCNSL, the reports of LC concomitant with MRI-confirmed spinal cord involvement are scarce. We herein report two patients with LC accompanied by intramedullary spinal cord lesions. The radiological and clinical findings of these two patients present a diagnostic dilemma of isolated intramedullary spinal cord lesions, and suggest that tumor infiltration between the spinal cord and brain may occasionally appear in patients with LC.

Case Reports

Case 1

A 37-year-old immunocompetent man presented with a three-month history of left leg paresis accompanied by paresthesia of the right leg. Thoracic spinal cord MRI showed a...
The diffuse infiltrating lesions in the cerebral white matter, bilateral internal capsules and splenium on FLAIR images without gadolinium contrast enhancement was noted. (D) The white matter lesions were expanded on the FLAIR images. (J) Gadolinium-enhancing nodular lesions were present in the frontal lobe and splenium. (E) The swollen hyperintense lesion on T2-weighted images disappeared, and the remaining spinal cord showed slight atrophic changes. (K) Gadolinium enhancing lesions were not seen in the spinal cord. Possible artifacts related to screw placement in the vertebrae were encountered as hypo-intense lesions. (F) Diffuse atrophic changes were observed in the brain. The diffuse hyperintense lesions were reduced on FLAIR images as compared with those in (D). (L) The gadolinium-enhancing nodular lesions seen in (J) were not identified. (A, G): Three months after the initial symptoms. (B, C, H, I): Five months after the initial symptoms. (D, E, J, K): Eight months after the initial symptoms. (F, L): Eleven months after the initial symptoms.

Figure 1. The thoracic spinal cord and brain MRI in Case 1 (A). A hyperintense lesion in the intramedullary spinal cord on T2-weighted imaging. The spinal cord was slightly swollen. (G) Gadolinium enhancement of the lesion. (B, C) Diffuse hyperintense lesions appeared in the cerebral white matter, bilateral internal capsules and splenium on FLAIR images. (H, J) No abnormal contrast enhancement was noted. (D) The white matter lesions were expanded on the FLAIR images. (J) Gadolinium-enhancing nodular lesions were present in the frontal lobe and splenium. (E) The swollen hyperintense lesion on T2-weighted images disappeared, and the remaining spinal cord showed slight atrophic changes. (K) Gadolinium enhancing lesions were not seen on the spinal cord. Possible artifacts related to screw placement in the vertebrae were encountered as hypo-intense lesions. (F) Diffuse atrophic changes were observed in the brain. The diffuse hyperintense lesions were reduced on FLAIR images as compared with those in (D). (L) The gadolinium-enhancing nodular lesions seen in (J) were not identified. (A, G): Three months after the initial symptoms. (B, C, H, I): Five months after the initial symptoms. (D, E, J, K): Eight months after the initial symptoms. (F, L): Eleven months after the initial symptoms.

The diffuse infiltrating lesions on T2-weighted images with gadolinium contrast enhancement (Fig. 1A, G). Spinal cord biopsy specimens obtained four months after onset showed non-diagnostic histopathological findings. Five months after the initial symptoms, brain MRI showed diffuse hyperintense lesions in the cerebral white matter, bilateral internal capsules, splenium and brainstem on fluid-attenuated inversion recovery (FLAIR) images without gadolinium contrast enhancement (Fig. 1B, C, H, I). As a decline in cognitive function began seven months after the initial symptoms, he was referred to our department. On examination, he showed mild cognitive impairment, paresis of the right arm and spastic paralysis of the left leg. The diffuse infiltrating lesions in the white matter had expanded, and a contrast-enhancing lesion appeared in the frontal white matter and splenium (Fig. 1D, J); however, the gadolinium-enhancing spinal cord lesion was diminished, and slight atrophy had developed in the spinal cord (Fig. 1E, K). Laboratory findings, including the serum lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) levels, were within the normal range. Anti-nuclear and anti-aquaporin-4 antibodies were negative. There was no evidence of infectious disease, sarcoidosis, inflammatory disease or malignant disease on systemic investigation. Furthermore, the autoantibodies associated with paraneoplastic neurological syndrome (anti-HuD, Yo, Ri, CRMP5, amphiphysin, Mal1, M2) were not detected by a Western blot analysis (ravo PNS Blot; ravo Diagnostika GmbH, Freiberg, Germany).

A cerebrospinal fluid (CSF) examination showed an increased protein level (100 mg/dL) with pleocytosis (cell count of 30/μL); however, B-cell malignancy was not detected on repeated cytology, flow cytometry or in the analyses of clonally rearranged immunoglobulin heavy-chain genes. The oligoclonal band was negative. Although gadolinium-enhancing lesions of the splenium are frequently observed in PCNSL, we could not exclude the possibility of steroid-responsive inflammatory diseases. High-dose corticosteroid therapy initially ameliorated his symptoms, but his condition gradually worsened despite repeated high-dose administration of corticosteroids.

To obtain a definitive diagnosis, a brain biopsy of the gadolinium-enhancing lesion in the frontal lobe was performed. The neuropathological findings showed scattered infiltration of atypical cells, with enlarged irregularly-shaped nucleoli (Fig. 2A). Mitotic cells were also present. An immunohistochemical examination showed that the atypical cells were positive for CD20 (Fig. 2B). The pathological diagnosis was therefore diffuse large B-cell lymphoma
intense lesions were partially reduced (Fig. 3C, D, I, J). Al-
sions almost completely disappeared and the FLAIR hyper-
symptoms gradually improved. The gadolinium-enhanced le-
oid treatment. She was then referred to our hospital, and a
sciousness rapidly appeared two weeks after corticoster-
tially ameliorated her symptoms, subsequent disturbances in
was negative. Although high-dose corticosteroid therapy in-
with pleocytosis (cell count of 23/μL). The oligoclonal band
amination showed an increased protein level (45 mg/dL)
inflammation during a systemic investigation. The CSF ex-
evidence of infection, sarcoidosis, malignant disease or other
sIL-2R levels were within the normal range. There was no
was not found on spinal cord MRI. The serum LDH and
perintense lesions of the white matter and the cerebellar
enhancing lesions were also present within the diffuse hy-
matter, bilateral internal capsules, brainstem and cerebellar
showed diffuse hyperintense lesions in the cerebral white
two-month history of headache and vertigo. Brain MRI
pression has persisted for more than two years.

Case 2

A 45-year-old immunocompetent woman presented with a
two-month history of headache and vertigo. Brain MRI
showed diffuse hyperintense lesions in the cerebral white
matter, bilateral internal capsules, brainstem and cerebellar
peduncle on FLAIR images (Fig. 3A, B). Gadolinium-
complished her symptoms, subsequent disturbances in
involvement of the white matter and the cerebellar
peduncles (Fig. 3G, H). An intramedullary spinal cord lesion
was not found on spinal cord MRI. The serum LDH and
levels were within the normal range. There was no
evidence of infection, sarcoidosis, malignant disease or other
inflammation during a systemic investigation. The CSF ex-
amination showed an increased protein level (45 mg/dL)
with pleocytosis (cell count of 23/μL). The oligoclonal band
was negative. Although high-dose corticosteroid therapy in-
ially ameliorated her symptoms, subsequent disturbances in
sciousness rapidly appeared two weeks after corticoster-
treatment. She was then referred to our hospital, and a
brain biopsy was performed. The neuropathological diagno-
sis was DLBCL.

The patient underwent whole brain irradiation, and her
symptoms gradually improved. The gadolinium-enhanced le-
sions almost completely disappeared and the FLAIR hyper-
intense lesions were partially reduced (Fig. 3C, D, I, J). Al-
though her brain lesions were improved, she subsequently
developed left paresis. Spinal cord MRI showed a hyperin-
tense lesion on T2-weighted images with gadolinium con-
trast enhancement (Fig. 3E, K). After spinal cord irradiation,
the left paresis was improved and the spinal cord lesion had
mostly disappeared (Fig. 3F, L). She additionally underwent
chemotherapy with methotrexate. She had a relapse in the
spinal cord eight months after the initial symptoms and was
treated with high-dose chemotherapy following autologous
peripheral stem cell transplantation. After the treat-
ment, remission has persisted for more than four years.

Discussion

We herein presented two cases of LC accompanied by in-
tramedullary spinal cord lesions. The clinical and radiologi-
features of Case 1 included that the patient initially
showed myelopathy caused by an isolated intramedullary
spinal cord lesion. The incidence of intramedullary lym-
phoma is exceedingly rare (6, 7, 9). Furthermore, isolated
spinal cord involvement is uncommon and observed in <1%
of cases of PCNSL (3). As the MRI findings of primary in-
tramedullary spinal cord lymphoma (PISCL) mimic those of
other causes of myelopathy, including demyelinating dis-
ease, Flanagan et al. described the characteristic MRI fea-
tures of PISCL as follows: 1) multifocal, 2) persistent
gadolinium-enhancement and 3) cauda equina or conus me-
dullaris involvement (7). Moreover, CSF findings of mark-
edly elevated protein levels (>100 mg/dL), a lack of oligo-
clonal bands and an elevated cell count were also proposed
as diagnostic clues, because they discriminate lymphoma
from multiple sclerosis (7). The preceding spinal cord lesion
in Case 1 regressed spontaneously, and this might have
complicated the early diagnosis and delayed appropriate
therapy. Alderson et al. reported four cases of contrast-
enhanced brain lesions with variable but non-diagnostic
histopathological findings that preceded the pathological di-
agnosis of PCNSL by several months, They called such pre-
ceding lesions ‘sentinel lesions’ (10). We could not fully
conclude whether the spinal cord lesion in Case 1 was a
‘sentinel lesion’. However, our case progressively deterio-
rated without a remission, which was typically seen in other
cases with sentinel lesions.

A relationship between an intramedullary spinal cord le-
lesion remains unknown, the good response to radiation noted in Case 2. Although the pathology of the spinal cord lesion and cerebral diffuse tumor cell infiltration also was noted in Case 2. Although the pathology of the spinal cord lesion remains unknown, the good response to radiation therapy suggested that it was a malignant tumor, rather than a demyelinating lesion (11). The route of tumor infiltration in these cases remains unclear. Two routes of tumor metastasis have been speculated: one is direct intraparenchymal invasion, and the other is dissemination via the CSF (8). Intraparenchymal invasion may have occurred in our patients, although signal changes visible on MRI were not detected. Alternatively, CSF pleocytosis was found in our patients, representing one of the possible aspects of meningeal dissemination (12); however, we failed to detect evidence of tumor meningeal dissemination. Nevertheless, our findings and those of recent studies suggest that central nerve system (CNS) lymphoma may be a whole brain disease, despite the fact that it presents as a solid mass in one or more locations. The clinical and radiological findings of our current patients indicate that patients with leukoencephalopathy or an isolated intramedullary spinal cord lesion of unknown etiology should be considered to have possible CNS lymphoma, representing a disease of the whole CNS.

We also reviewed the radiological and clinical findings of a series of 11 consecutive immunocompetent patients with PCNSL treated in our hospital from 2008 to 2011 (unpublished data). All pathological diagnoses were DLBCL, and radiological findings of cerebral diffuse white matter lesions were confirmed in three cases (Case 1, Case 2, and a case not presented here). Among the three patients with PCNSL, two (Cases 1 and 2) showed MRI-confirmed intramedullary spinal cord involvement. Based on these clinical and radiological findings, it is possible that tumor infiltration between the spinal cord and brain may occur in the course of the disease process in LC, and that the frequency of these findings may be relatively higher than has been previously considered.

In conclusion, we herein presented two cases of LC with intramedullary spinal cord involvement. Further studies involving larger numbers of patients with PCNSL accompanied by intramedullary spinal cord lesions are needed to clarify their clinical and radiological features. Physicians should be aware that LC may be a differential diagnosis of leukoencephalopathy, and should be treated as a disease of the whole CNS with spinal cord involvement.

The authors state that they have no Conflict of Interest (COI).

References


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