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【 CASE REPORT 】

Intravascular Lymphoma Presenting as a Cavernous Sinus Tumor

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Abstract:
Intravascular lymphoma (IVL) is a malignant lymphoma that lacks the expression of cell surface adhesion molecules so that cells fluidly migrate within the blood vessels. The patient in the present study had restricted eye movement caused by IVL, mimicking a cavernous sinus tumor. Because the cavernous sinus lumen is divided into multiple compartments by trabeculae and venous channels, IVL tumor cells were trapped in these compartments, thus forming a mass, which subsequently extended into the contralateral cavernous sinus via the anterior and posterior intercavernous sinuses. This is a rare case of IVL forming a mass inside the cavernous sinus.

Key words: intravascular lymphoma, cavernous sinus, biopsy

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Introduction

Intravascular lymphoma (IVL) is a subtype of malignant lymphoma characterized by the proliferation of large lymphoma cells within the lumina of small blood vessels. It is definitively diagnosed when large lymphoma cells are localized within small blood vessels. In advanced lesions, IVL can diffusely invade extravascular tissues or form a mass (1). The diagnosis of IVL is difficult because of the characteristic nature of these tumor cells which lack the expression of cell surface adhesion molecules, such as CD29 and ICAM1 (CD54) and, therefore, do not adhere to the vessel wall (2) and fluidly migrate through the lumina of blood vessels without lingering at the same site. In some cases, the cells proliferate within the blood vessels, thereby potentially occluding them and causing ischemia without any evidence of tissue invasion or the formation of a mass. Kinoshita et al. (3) investigated the histopathological differences between the primary central nervous system (CNS) malignant lymphoma and IVL and reported that IVL cells lack the expression of matrix metalloproteinase (MMP) 2 and MMP9 involved in the extravascular invasion of tumor cells. Therefore, the absence is associated with the inability of IVL cells to infiltrate into extravascular tissues.

Although a pathological diagnosis based on biopsies is necessary to definitively diagnose IVL, the success of this approach is poor because of the nature of these tumor cells (4). In the absence of clearly detectable lesions, random skin biopsies are also recommended (5). An antemortem diagnosis of IVL in the CNS is difficult because of the difficulty in accessing that region. We herein present a rare case of a successful diagnosis of IVL which had formed a mass inside the cavernous sinus.

Case Report

A 42-year-old woman presented to an ophthalmology clinic with right ptosis and diplopia on left gaze, but without any symptoms of headache or ophthalmalgia. She was re-

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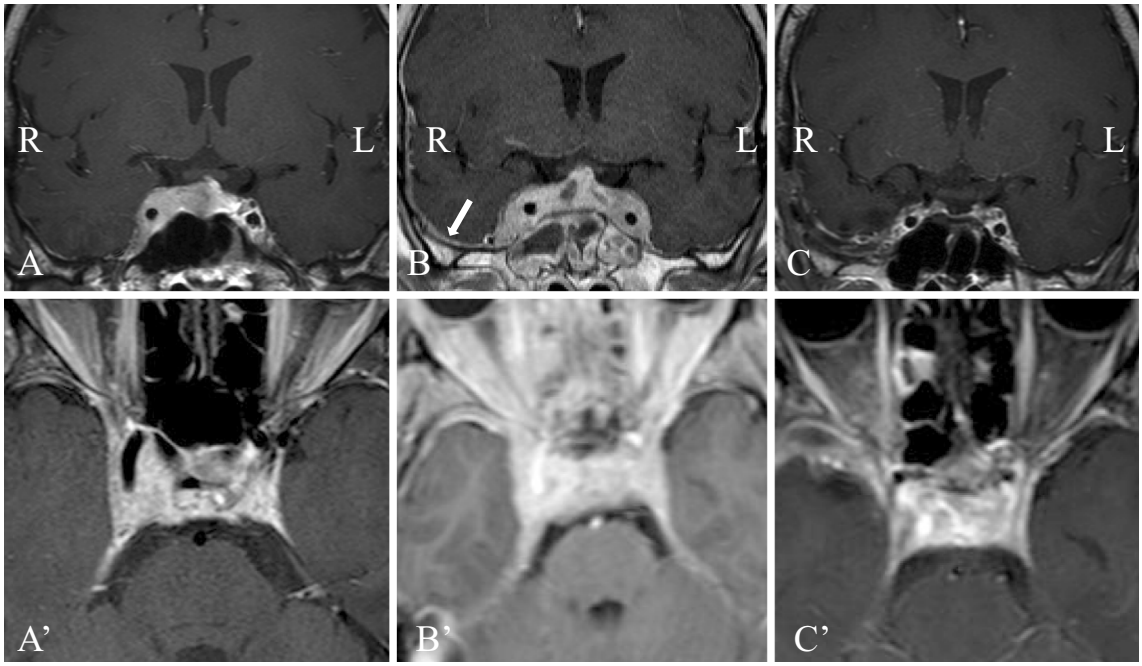

Figure 1. **A-A': Coronal (A) and axial (A') sections of contrast-enhanced magnetic resonance imaging (MRI) before the initial surgery. A mass is seen extending from the right cavernous sinus to the pituitary region. B-B': Coronal (B) and axial (B') sections of contrast-enhanced MRI before the second surgery. A new mass is evident in the left cavernous sinus. White arrow indicates the dura matter adjacent to the cavernous sinus that is hypertrophied and enhanced compared with the previous MRI (A). C-C': Coronal (C) and axial (C') sections of contrast-enhanced MRI obtained 1 year after treatment was begun. The tumor has completely disappeared.**

ferred to our neurology department 2 weeks thereafter. On neurologic examination, she had right mydriasis and the primary position of her right eye was laterally deviated. There was a restriction of elevation, depression, and adduction of the right eye; hence, the right eye could not cross over the midline, and intortion and extortion were also not observed. Her left eye exhibited neither any abnormalities nor any other cranial nerve deficits. Brain magnetic resonance imaging (MRI) revealed a mass that filled the right cavernous sinus and extended to the pituitary, which was homogeneously enhanced with gadolinium (Fig. 1A). There were no abnormalities on blood tests, including basal pituitary hormone levels or tumor markers. The concentrations of soluble interleukin-2 receptor (sIL2R) at 233 U/mL (reference value: 121-613 U/mL) and lactate dehydrogenase (LDH) at 169 IU/L were all within the normal limits. The cerebrospinal fluid (CSF) had a cell count of 1/μL, total protein level of 39 mg/dL, glucose level of 60 mg/dL (with a simultaneous blood glucose level of 106 mg/dL), and an opening pressure of 10.5 cmH_2O. She was thereafter admitted to the neurosurgery department with a tentative diagnosis of pituitary adenoma and apoplexy. Trans-sphenoidal pituitary decompression and biopsy were performed, which did not improve her ophthalmologic signs. The pathology report on the biopsy specimen was normal pituitary tissue with lymphocytic infiltrate (Fig. 2). Immunohistochemical staining showed no T or B lymphocyte monoclonality. There was no T lymphocyte gene rearrangement. She was given dexamethasone to treat edema and was discharged home with a close outpatient follow-up.

She was readmitted to the neurology department 1 month later because her eye symptoms had extended to the left side. Neurologic examination revealed total right ophthalmoplegia, loss of sight in the right eye, marked edema of the right palpebrae and conjunctiva, and complete ptosis with exophthalmos. A fundus examination revealed venous dilation of the right fundus, suggesting central retinal vein occlusion. Visual acuity in the left eye was reduced to counting fingers. There was left ptosis and failure of adduction, elevation, depression, intortion, and extortion. Blood tests showed dramatically increased levels of sIL2R (3,326 U/mL) and LDH (784 U/L). A bone marrow biopsy was performed, and the specimen was reported to be normal. Because of the rapidly deteriorating clinical condition and increasing size of the mass, an infection was suspected. However, tests for C-reactive protein, β-D-glucan, interferon-gamma release assays, and whole body computed tomography were all normal. A CSF examination showed a normal cell count (0/μL), elevated total protein level (73 mg/dL), and normal glucose level (69 mg/dL, with a simultaneous blood glucose level of 118 m/dL). Brain MRI revealed that the mass had increased in size and extended from the right to the left cavernous sinus. The dura mater adjacent to the cavernous sinus was enhanced with gadolinium (Fig. 1B-B'). Fluorodeoxyglucose-positron emission tomography showed a high uptake localized to the cavernous

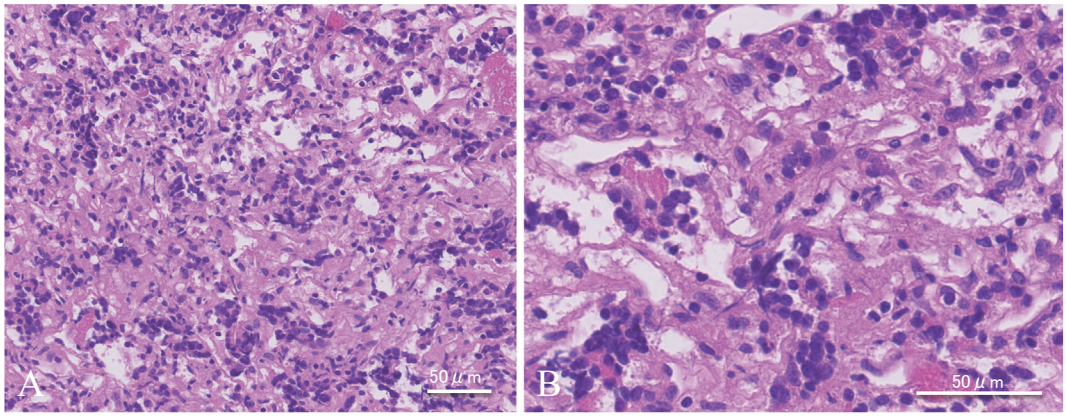

Figure 2. **Histopathologic findings from the initial surgical biopsy. Hematoxylin and Eosin staining of a tumor specimen demonstrating lymphoid infiltrates. The lymphocytes do not appear to be atypical. Original magnifications: A ×200, B ×400.**

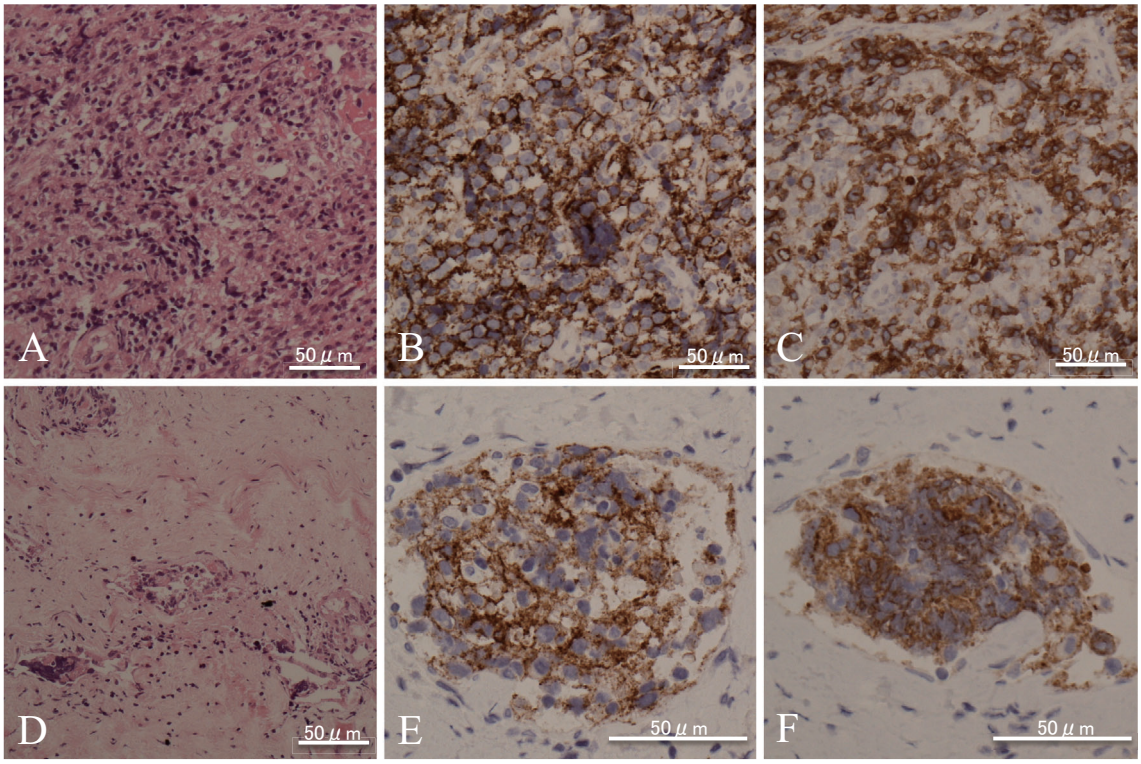

Figure 3. **Histopathological findings of specimens from the second surgery. Lymphocytes with nuclear atypia diffusely infiltrate the cavernous sinus (A-C). Immunostaining indicates that the cells are positive for CD20 (B) and CD79α (C). The vascular lumen of vessels from the dural biopsy is filled with tumor cells similar to those in the cavernous sinus (D-F). Immunostaining indicates positivity for CD20 (E) and CD79α (F). Original magnifications: A-D ×200 and E, F ×400.**

sinuses, with no uptake elsewhere in the body. The diagnostic hypothesis at that point was a localized malignant lymphoma within the cavernous sinus. A right fronto-temporal craniotomy was performed to carry out a biopsy of the lesion via an intracranial approach to the cavernous sinus. Intraoperatively, a milky-white mass was discovered in the cavernous sinus and was collected. Biopsy samples of the dura mater adjacent to the cavernous sinus were also collected. On histopathological examination, the mass was found to comprise diffuse large-B-cell lymphoma (DLBCL) cells, leading to a diagnosis of that type of lymphoma (Fig. 3A-C). However, similar large B-cell lymphoma cells were also detected within the blood vessels of the dura mater (Fig. 3D-F). Because no tumor cells were detected in the pituitary tissue and similar large-B-cell lymphoma cells were observed only in the cavernous sinus and within the dural blood vessels, a definitive diagnosis of intravascular diffuse large B-cell lymphoma was made. She was treated with a regimen comprising six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. At the

time of writing, 1 year after treatment was started, she had lost her sight in her right eye, but the extraocular movements in both eyes had recovered. No evidence of a tumor was seen on imaging, and the levels of sIL2R and LDH had normalized (Fig. 1C).

Pathology

The histopathological findings of the initial biopsy (Fig. 2) included lymphocytic invasion of the pituitary and prominent interstitial connective tissues. The invading lymphocytes did not appear to be atypical. Immunostaining for lymphocyte markers (CD3, CD5, CD20, and CD79α) showed no signs of monoclonality.

The biopsy results from the second surgery (Fig. 3) revealed lymphocytes with nuclear atypia diffusely infiltrating the cavernous sinus (Fig. 3A-C). Immunostaining was negative for CD3 and CD5, but positive for CD20 and CD79α, leading to a diagnosis of DLBCL. Similar tumor cells were found filling the vascular lumina in the dural biopsy specimen (Fig. 3D-F).

Discussion

The mass observed in the present case is not consistent with the usual findings in IVL, which may be attributable to the anatomical features of the cavernous sinus. The lumen of the sinus is divided into multiple compartments by trabeculae and venous channels. Tumor cells may become trapped in some of these compartments rather than being swept away by the bloodstream (6, 7). It was postulated that trapped tumor cells had proliferated and then serially spread into new compartments, consequently filling the right cavernous sinus and ultimately progressing to the contralateral side via the anterior and posterior intercavernous sinuses that communicate with the left and right sides.

Based on the above hypothesis, the progression of ophthalmic symptoms could be explained as follows. Inside the cavernous sinus, the tumor mass could have compressed the oculomotor and trochlear nerves to paralyze them; the cavernous sinus enlarged by the presence of the tumor cells could have compressed the optic nerve and central retinal vein to cause blindness and venous dilation, followed by tumor progression to the left side. Other possibilities are direct tumor invasion to those nerves; however, the exact mechanism of progression of the ophthalmic symptoms in this case remains unclear.

Although MRI suggested the possibility of tumor invasion of the pituitary, the histopathology of the gland only showed evidence of inflammation.

Extravascular progression is indeed observed in some cases of advanced IVL. However, in the present case, the tumor in the cavernous sinus induced inflammation of the surrounding tissues, resulting in a hypophysitis-like condition of the pituitary.

The specific structure of the cavernous sinus made the diagnosis difficult. The histopathological features of the cavernous sinus mass led to a diagnosis of DLBCL because we failed to show that tumor cells were restricted to the lumen of the blood vessels. This is understandable because there are no blood vessels within the cavernous sinus itself. The exact origin of this patient's IVL is therefore unclear.

Rizek et al. (8) described a similar case of IVL involving the pituitary presenting with ophthalmic dysfunctions. In this patient, the spread of IVL to the cavernous sinus from the pituitary could explain the ophthalmic symptoms. In our case, histopathologically, there was no evidence of IVL in the blood vessels in the pituitary. Because the first signs were oculomotor and trochlear palsy, it cannot be denied that the tumor cells arose from the blood vessels supplying those nerves and the pituitary. Another possibility is that the dural blood vessels initially contained the IVL cells that then extended to the cavernous sinus. In that case or if the IVL arose in some other place, the cells that reached the cavernous sinus nevertheless were trapped, thereby forming a mass that compressed the nerves and paralyzed them. However, this seems less likely because serial changes on MRI suggest that the dura mater involvement was relatively new. The histopathology of the dural biopsy indicated that the tumor cells were restricted to the blood vessels, thus confirming the diagnosis of IVL.

Conclusion

IVL is widely recognized as the proliferation of lymphoma cells within the lumina of the small blood vessels. This case suggests that IVL is present not only in the blood vessels themselves but also within any cavity formed by the blood vessels, such as the cavernous sinuses. Biopsy of the cavernous sinus alone may be insufficient to diagnose IVL because the blood vessels do not exist within the sinus itself. Therefore, biopsies of tissues including small blood vessels surrounding the suspected lymphoma might assist in making an accurate diagnosis.

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

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