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Case Report

Decreased Visual Acuity after Chemotherapy in a Case with Diffuse Large B Cell Lymphoma

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Abstract

A 53-year-old male with no past medical history presented with abdominal pain for 2 days, accompanied with fever and poor appetite. Leukoerythroblastosis along with elevated lactate dehydrogenase and a bone marrow exam led to the diagnosis of diffuse large B-cell lymphoma, germinal center B-cell (GCB) type. After the 5th cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, progressively decreased visual acuity along with left ptosis occurred. Drug-related optic neuropathy was suspected, and initial magnetic resonance imaging (MRI) and cerebral spinal fluid (CSF) studies revealed negative results. However, meningeal lymphomatosis with bilateral optic nerve infiltration was finally diagnosed by subsequent MRI and CSF studies after 1 month. This rare case highlights the pitfalls of CSF studies. Based on previous studies, an adequate sample (>10.5 ml), rapid processing within 1 h, and serial testing at least twice can improve the rate of positive results while reducing the false-negative rate. We hope that this case can remind clinicians of the possible diagnosis of lymphomatous optic nerve infiltration from systemic lymphoma, and that properly conducted CSF studies can help to avoid missing this diagnosis.

Keywords: Cerebral spinal fluid study, chemotherapy, diffuse large B cell lymphoma, lymphomatous optic nerve infiltration, meningeal lymphomatosis

Introduction

Primary central nervous system (CNS) lymphoma has ~20% chance of progressing with ocular involvement,[1] but it is rare in systemic non-Hodgkin lymphoma (NHL) without CNS involvement.[2] The diagnostic tools for malignant optic nerve infiltration include magnetic resonance imaging (MRI), cerebral spinal fluid (CSF) analysis, and optic nerve biopsy. Because this clinical situation is rare, the pitfalls of the diagnosis should be noted. Here, we present a case with the bone, liver, and spleen (BLS) type of diffuse large B cell lymphoma (DLBCL) who experienced visual loss and was finally diagnosed with meningeal lymphomatosis with optic nerve infiltration. The patient gave permission for this article to be published.

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Case Report

A 53-year-old male with no past medical history presented with abdominal pain for 2 days, accompanied with fever and poor appetite. A physical examination showed enlarged lymph nodes over bilateral neck and hepatomegaly, and a hemogram revealed pancytopenia (white blood cell [WBC]: 2.20 × 10^3, hemoglobin: 8.8 g/dl, and platelets: 73 × 10^3) along with leukoerythroblastosis (differential blood count: band: 3%, metamyelocyte: 1%, myelocyte: 4%, and normoblast: 5/100 WBC) and elevated lactate dehydrogenase that led to the diagnosis of DLBCL, germinal center B-cell (GCB)type with positive CD10, and highly expressed MYC (>80%, strong) in immunohistochemical staining through a bone marrow biopsy. Positron emission tomography/computed tomography (PET-CT) demonstrated that the involved lesions incorporated almost all bones, marrow, liver, and spleen, so the DLBCL was regarded as being the BLS type, Stage IV with four International Prognostic Index factors. The PET-CT implicated extensive bone marrow infiltration by lymphoma, explaining the pancytopenia with leukoerythroblastosis. Finally, since the whole clinical picture could be explained by DLBCL BLS type and only mildly enlarged neck lymph nodes were revealed through CT, an additional lymph node biopsy was not performed at that time [Figure 1]. The patient then received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) treatment. After 4 cycles of treatment, the fever, abdominal pain, and poor appetite were improved along with a normal hemogram exam. However, around the period of the 5th cycle of treatment, the left eye ptosis occurred for a couple of days, accompanied by the left eye mildly and involuntarily turning downward and outward with left pupil dilation to 5 mm in size, which implicated a lesion of cranial nerve III. Nevertheless, the brain MRI with/without gadolinium did not show any lesions. In addition, the CSF cytology exam did not show any lymphoma cells, and it showed normal biochemical results without any evidence of infection. The fatigue maneuvers (sustained upgaze test) and acetylcholine receptor antibodies were negative, ruling out myasthenia gravis. One month later, the left ptosis and limited extraocular muscle function progressed along with bilateral visual impairment. The best-corrected visual acuity assessed by an ophthalmologist showed that the right was counting fingers at 50 cm and the left was nearly complete vision loss at the worst situation. Findings of intraocular pressure, fundus, and anterior segment of the eyeballs were unremarkable. MRI was then performed again, which showed edema along bilateral optic nerves and sheaths, which raised the suspicion of newly developed inflammatory change or tumor involvement. There were no ischemic changes or mass-like lesions in this image study. CSF at this time showed increased large lymphoid cells with nucleoli, indicating meningeal lymphomatosis with optic nerve infiltration [Figure 1]. A chemotherapy regimen with cyclophosphamide, dexamethasone, methotrexate, doxorubicin, vincristine, and cytarabine (hyper-CVAD), triple intrathecal chemotherapy (hydrocortisone, cytarabine, and methotrexate) along with rituximab intrathecal therapy were given. After treatment, his visual acuity gradually improved within 1 month [Figure 2].

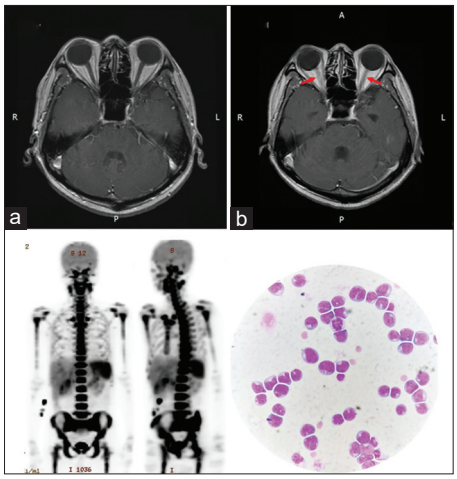

Figure 1: (a) Initial T1-weighted contrast-enhanced magnetic resonance imaging brain images in axial view, showing no obvious lesions at the optic nerves, but 1 month later, (b) bilateral optic nerve edema was demonstrated (arrows). Positron emission tomography-computed tomography revealed 18F-fluorodeoxyglucose uptake throughout the skeleton, incorporating marrow, lymph nodes in bilateral neck, and the liver and spleen. Lymphoma cells in cerebral spinal fluid were found in microscope examinations (×1000)

Discussion

This patient experienced left ptosis along with a progressive decline in bilateral visual acuity after the 5th cycle of R-CHOP. Ptosis can occur at unilateral or bilateral sites and be classified as acquired or congenital onset, depending on the age at onset. The mechanism of ptosis includes disorders of aponeurosis, muscles, neurons, and neuromuscular junction.[3] As for unilateral acquired ptosis as in our case, it seems unlikely that this was due to an aponeurotic cause because there was no atrophy of the skin, atrophy of fat of the upper lid, or obvious levator palpebrae muscle dysfunction. Besides, MRI did not find obvious muscle atrophy of the orbital muscle, reducing the likelihood of myogenic causes of ptosis, and no mass-like

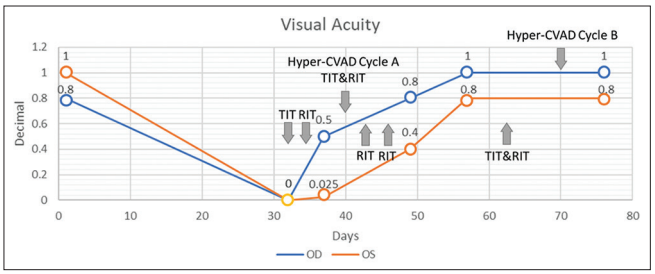

Figure 2: The patient's visual acuity worsened over a month, and after the treatment with Hyper-CVAD and intrathecal chemotherapy it gradually improved. TIT: Triplet intrathecal chemotherapy: Methotrexate, cytarabine, hydrocortisone. RIT: Rituximab intrathecal chemotherapy. The yellow circle indicates that the visual acuity could not be measured using the acuity chart, the visual acuity of OD was counting fingers at 50 cm and that of OS was loss of light perception

lesions were discovered, which could be a cause of nerve palsy. Myasthenia gravis as a neuromuscular junction disorder was also ruled out as mentioned above. Therefore, based on these findings, the neurological examination supported a possible infiltrating lesion over cranial nerve III and optic nerve (cranial nerve II) lesion. In addition, with this kind of asymmetric involvement, lymphoma infiltration seemed to be a reasonable differentiation diagnosis.

From another approach regarding the visual loss, the differential diagnosis included drug-related optic neuropathy, CNS infection or inflammation, and lymphoma infiltration. In this case, cyclophosphamide, doxorubicin, and vincristine were the possible offending drugs responsible for optic neuropathy. Ptosis along with optic nerve neuropathy has also been reported to be a side effect of vincristine.[4] Without any evidence of infection or lymphoma infiltration, observation was decided initially in this case. However, visual acuity progressed, and finally, meningeal lymphomatosis with optic nerve infiltration was diagnosed.

The main diagnostic tools for optic neuropathy include MRI, CSF analysis, and optic nerve biopsy. MRI can clearly distinguish between meningeal, cerebrospinal fluid, and axonal portions of the optic nerve, but the findings are nonspecific.[5] Imaging findings can be used to differentiate between primary optic nerve tumors such as optic glioma and optic nerve sheath meningioma, inflammatory disorders such as multiple sclerosis or sarcoidosis, infections such as syphilis or tuberculosis, and second malignant infiltration as in our case.[5-8] Clinical findings are still essential for the final diagnosis, regardless of the added information of MRI findings.

CSF studies are a useful diagnostic tool in this situation, and they can lead to a definitive diagnosis. However, because lymphomatous optic nerve infiltration (LONI) comprises about 5% of secondary optic nerve tumors,[9] the possibility of false-negative results of CSF studies should be noted in this rare situation. Although in the review by Myers *et al*.[10] the cases of LONI from B cell NHL did not necessarily demonstrate malignant cells in CSF, this may depend in part on differences in clinical practice, and thus the pitfalls of this exam are worth noting. The sensitivity of CSF cytology varies widely (2%–32%).[11] A larger volume (≥10.5 mL) and analyzing serial CSF samples can improve sensitivity. A second lumbar puncture has been shown to yield a higher rate of positive CSF analysis, while little added benefit from a third lumbar puncture has been reported.[12] After CSF is withdrawn, the preserved cells will decrease quickly within an hour, and thus processing the sample immediately can also reduce the false-negative rate, while delayed processing can increase the false-negative rate by up to ~36%.[12,13] Based on these findings, it is important to increase the number of CSF studies and immediately process the sample with an adequate amount. Negative MRI findings and first CSF exams cannot preclude LONI, and improvement of sample processing can increase the chance of an early diagnosis.

An optic nerve biopsy is indicated when an optic nerve disease causes significant loss of vision despite empiric treatment and negative results of systemic investigations. The methods include image-guided fine-needle aspiration biopsy, transconjunctival biopsy, and a neurosurgical approach.[14] A Transconjunctival biopsy is a minimally invasive and safe technique, which can be considered if the facility is available in the hospital.[15]

In conclusion, LONI cannot be ignored in systemic lymphoma, and the pitfalls of CSF analysis should be noted to achieve a higher true-positive rate. We hope that this case can remind clinicians of the possible diagnosis of LONI, and that properly conducted CSF studies can help to avoid missing this diagnosis.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent form. In the form, the patient has given his consent for the images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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