原 著

Discrepancy between magnetic resonance imaging and cranial nerve neuropathies associated with the involvement of diffuse large B-cell lymphoma (DLBL)

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Running title：Discrepancy between MRI and CN neuropathies in DLBL

Key words：cranial nerve —— diffuse large B-cell lymphoma —— prednisolon —— neuropathy —— R-CHOP

Abstract

An 83-year-old female developed diffuse large B-cell lymphoma (DLBL) of the left nasal cavity. Complete remission was achieved after two courses of Rituximab and CHOP (R-CHOP). During the fourth course of R-CHOP, sensory disturbance and palsy of the left face developed. Left trigeminal nerve swelling was observed in magnetic resonance imaging (MRI) followed by double vision in the left eye, and MRI revealed swelling of both trigeminal nerves but not of the abducens nerve. Although the swelling of the trigeminal nerves and the double vision subside after administration of prednisolone, the palsy of the left face persisted. Two months after the fourth course of R-CHOP, symptoms of the palsy of the left face progressed and palsy of the right face, double vision, and palsy of the left facialis nerve developed. Then, blepharoptosis of the right eye developed and palsy of the right oculomotorius nerve was observed. MRI showed the presence of trigeminal nerve and oculomotorius nerve swelling but no swelling of the other cranial nerves. Furthermore, skin eruption developed around the left eye. Cytology of this lesion revealed the invasion of lymphoma cells.

Introduction

Infiltrative cranial nerve neuropathies from non-primary central nervous system lymphoma is uncommon；a few cases have been reported, however, revealing invasion into the trigeminal nerve and other manifesting symptoms [1-3]. Cranial nerve neuropathies aggravate with the disease's progression [1,3], although imaging examinations are insufficient for dissecting the correlation between the neural invasion and the clinical symptoms. The presented case developed diffuse large B-cell lymphoma (DLBL) of the left nasal cavity, and recurrence was observed with the infiltration of trigeminal nerves after complete remission. The primary finding was paralleled the initial detection of symptoms by magnetic resonance imaging (MRI). As the symptoms progressed, however, neuropathy did not exactly parallel the MRI findings following the administration of prednisolone. These facts suggest that the continuous neuropathy was caused by the persistent invasion of lymphoma cells, even though the MRI produced normal findings.

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Case Report

An 83-year-old woman was referred to our hospital, suffering sniffles and nose bleeds. On admission, her red blood cell count was 444×10^{10}/l, hemoglobin level was 13.1g/dl, leukocyte count was 3.6×10^{9}/l (stab and segmented neutrophils：56%, monocytes：10%, eosinophils：8%, lymphocytes：24%), platelet count was 17.7×10^{10}/l, lactate dehydrogenase (LDH) was 194 IU/l, and C-reactive protein level was 1.2mg/dl (normal range is below 0.3mg/dl). The serum soluble interleukin-2 receptor (sIL-2R) level in this case was 1670 U/ml (normal range is from 145 to 519). The biopsy specimen of the left nasal cavity revealed DLBL. Swelling in both neck lymphnodes without the other lymphnodes was also observed. The patient's performance status (PS) according to ECOG was grade 0, clinical stage was II, and the International Prognosis Index (IPI) at onset was low grade.

The patient was treated with a 70% dosage of CHOP (cyclophosphamide 750mg for one day, adriamycin：50mg for one day vincristine：1.4mg for one day, prednisolone：60mg for 5days) plus rituximab (375mg/m^2 for one day). A complete remission was achieved after two courses of R-CHOP. Sensory disturbance, which was dominant in the trigeminal nerves, and palsy of the left face, developed at the time of the fourth course of R-CHOP. Slight swelling of the left trigeminal nerve was visible in MRI (Fig. 1A：5/6 2003). There were no abnormal cells observed in the central spinal fluid (CSF). The symptoms subsequently progressed, with double vision of the left eye developing two weeks after the first symptoms, which both trigeminal nerves but not the abducens nerve showed swelling in MRI (Fig. 1B：5/23). Thirty milligrams of prednisolone was administered and the double vision disappeared despite the persistence of palsy in the left face. Prednisolone was tapered to 15 mg for the administration of maintenance therapy, and the swelling of the trigeminal nerves subsided according to MRI (Fig. 1C, 1D：6/3, 7/1). However, the palsy of the left face progressed and palsy of the right face (right trigeminal nerve), double vision, and palsy of the left facialis nerve developed two months after the fourth course of R-CHOP, though only the right trigeminal nerve showed swelling in MRI (Fig. 1E：7/22). Subsequently blepharoptosis of the right eye and palsy of the right oculomotorius nerve developed. According to MRI, the right trigeminal and right oculomotorius nerves swelled, but none of other cranial nerves did (Fig. 1F：8/22).

Lumbar puncture was performed and mononuclear cells were observed in a CSF. A skin eruption gradually developed around the left. The cytology of this lesion revealed the invasion of lymphoma cells (Fig. 2). Taking these facts into consideration, the cranial neuropathies were diagnosed as being associated with the invasion of DLBL. Since the patient was not willing to take additional chemotherapy and radiotherapy, only supportive care was provided. The MRI of September 12 showed swelling of both trigeminal and the right oculomotorius nerves (Fig. 1G). The patient then gradually lost consciousness and died due to the disease progression on November 18. Throughout her clinical course, lymphoma was under control without the lesion of cranial nerves.

Discussion

Infiltrative cranial nerve neuropathies from nonprimary central nervous system lymphoma are rare, and the first symptom of involvement of a trigeminal nerve in primary or relapsed non-Hodgkin's lymphoma (NHL) is also rare [1-3]. Various clinical investigations have not always been able to identify an obvious cause for these neuropathies.

In this case, a skin biopsy from the facial skin eruption revealed the infiltration of DLBL. Furthermore, the first clinical symptoms and the MRI findings revealed the involvement of the left trigeminal nerve, which was connected to the tumor by the ethmoidalis anterior nerve in the left nasal cavity. These findings led us to the conclusion that the cranial neuropathies and facial skin eruption were due to the progression of DLBL.

A discrepancy was observed between the clinical symptoms and the MRI results, with possible causes being the infiltration of DLBL as well as inflammation of the cranial nerves. Alternatively, the invisible infiltration of DLBL, which is enough to induce clinical symptoms, might have caused

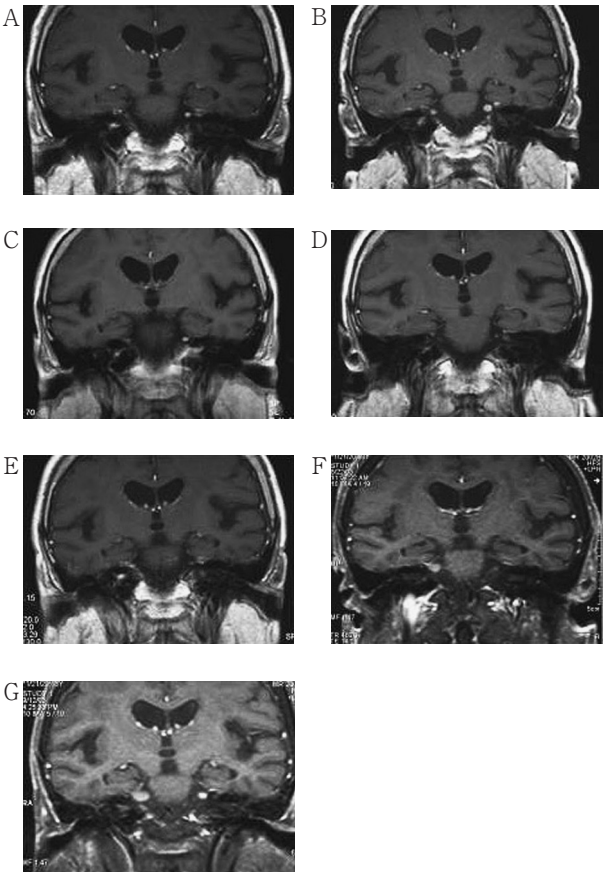

Fig. 1. T1 images demonstrated with or without gadolinium enhancement of the brain MRI.

A. Neurological symptoms in the dominant trigeminal nerve developed at the time of the fourth R-CHOP course on May 6. 2003. The left trigeminal nerve swelled slightly.

B. Double-vision of the left eye developed two weeks after the first symptoms. Both trigeminal nerves but not the abducens nerve swelled on May 23.

C. Recovery of the swelling of both trigeminal nerves observed after administration of prednisolone on June 6.

D. The swelling of both trigeminal nerves disappeared on July 1.

E. Only the right trigeminal nerve was swollen when the new neurological symptoms developed on July 22.

F. The right trigeminal and right oculomotorius nerve were swollen when blepharoptosis of the right eye and palsy of the right oculomotorius nerve developed on August 22.

G. Both trigeminal and right oculomotorius nerves were more swollen on September 12.

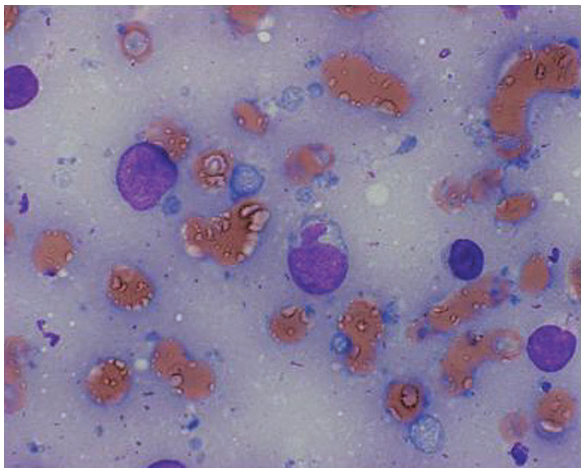

Fig. 2. Cytology of the skin erruption around the eye. The cytology of this lesion revealed the invasion of lymphoma cells.

this discrepancy. In this case, we have to imagine such a condition by the discrepancy between the MRI finding and the clinical symptoms; since prednisolone inhibited the infiltration of DLBL, the accompanying inflammation might be improved. Harris et al. reported the paraneoplastic syndrome of orbital myositis and cranial neuropathies [3]. In this case, administration of prednislone cleared the swelling of the trigeminal nerve at first, although symptoms were and cranial nerve swelling recurred with disease progression. These facts suggested that the paraneoplastic syndrome in the swelling of the trigeminal nerves possibly occurred at first and that the persistent symptoms and later cranial nerves swelling were due to the involvement of the DLBL.

The characteristics of primary or recurrent NHL patients who developed their first symptom with trigeminal nerve involvement are shown in Table 1. NHL involvement with CSF was not developed during the diagnosis, and direct invasion or a primary tumor were also considered. In lymphomatous meningitis, headache, nausea, vomit, and peripheral neuropathies of proximal sites was common [4-9]. In this case, the neurological findings suggested the invasion of DLBL into cranial nerves (such as the trigeminal nerves and facial nerves) at the distal levels, although no histological examination was carried out. This might be one of the reasons for the difficulty of diagnosing NHL invasion into the trigeminal nerves when the primary tumor was

Table 1　Result of reported cases who developed cranial nerve lymphoma involvement

Age	Pathology	Gender	Another lesion at diagnosis	L/N swelling at diagnosis	CNF invasion at diagnosis	Impairment at onset of CN	CN involvement by image	Treatment	Outcome
22y	Burkitt	Male	Ethmoid and sphenoid sinus	neg	neg	Trigeminalnerve V1(both), V2(both)	MRI:ND, CT:neg	chem+radi	18week/died
14y	Burkitt	Male	Nasopharyngeal	neg	neg	Trigeminalnerve(R)	MRI:ND, CT:unk	chem+radi	alive (relapse 2 times)
43y	DLB	Male	Extra ocular muscle	neg	neg	Trigeminalnerve V3(R), V6(R), V7(L)	MRI:neg CT:neg	chem	11month/died
83y	DLB (presented case)	Female	Nasopharyngeal	pos	neg	Trigeminalnerve(L)	MRI:pos CT:pos	chem	9month/died

Abbreviations used in this table:DLB:diffuse large B cell lymphoma, neg:negative, pos:positive, ND:not done, unk:unknown, chem:chemotherapy, radi:radiation

hard to find. Furthermore, it was difficult to identify abnormalities in the cranial nerves upon examination of the image. Although MRI is more effective at detecting abnormalities of the cranial nerve than computed tomography (CT), it is often unable to detect cranial nerve involvement[3]. This was also true in the presented case, in which only the right trigeminal and oculomotorius nerve swelling were observed when many other neurological symptoms of the cranial nerves developed.

In conclusion, the discrepancy between the MRI findings and the clinical symptoms in this case might have been a result of inflammation due to DLBL. It is still difficult to diagnose NHL involvement with cranial nerves when the primary tumor is difficult to find. However, the NHL invasion of cranial nerves will be more readily detected with improvements in the imaging tools.

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