Primary Retroperitoneal Diffuse Large B-cell Lymphoma Presenting with Numb Chin Syndrome and Painful Ophthalmoplegia

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Abstract

Numb chin syndrome (NCS) and painful ophthalmoplegia (PO) are neurological syndromes associated with the disturbance of certain cranial nerves and their downstream nerves. These syndromes are caused by various diseases, and, in rare cases precede the diagnosis of systemic malignant lymphoma. We herein present the case of a 59-year-old man diagnosed simultaneously with NCS and PO caused by a tumor located around the cavernous sinus and with diffuse large B-cell lymphoma that was identified via biopsy of a large retroperitoneal tumor. He was successfully treated with a standard rituximab-containing chemotherapy combined with high-dose intravenous methotrexate and intrathecal chemotherapy.

Key words: diffuse large B-cell lymphoma, numb chin syndrome, painful ophthalmoplegia, central nervous system infiltration, primary retroperitoneal lymphoma, autologous peripheral blood stem cell transplantation


Introduction

Numb chin syndrome (NCS) is a sensory neuropathy characterized by numbness in the chin and lower lip caused by a functional disturbance of the mandibular distribution of the trigeminal nerve. Painful ophthalmoplegia (PO) refers to periorbital pain with ipsilateral ocular motor nerve palsies, which are often accompanied by oculosympathetic paralysis and/or sensory loss in the distribution of the ophthalmic and maxillary division of the trigeminal nerve. Both NCS and PO are consequences of the dysfunction of certain cranial nerves, and they sometimes precede the diagnosis of systemic malignancies such as malignant lymphoma. Theoretically, tumor infiltration around the cavernous sinus can involve several cranial nerves, such as the oculomotor nerve or trigeminal nerve, and can cause NCS as well as PO; however, such cases have so far only been sporadically reported.

We herein describe a case of primary retroperitoneal diffuse large B-cell lymphoma presenting with NCS and PO, all of which were well controlled with intensive intravenous and intrathecal chemotherapy containing rituximab.

Case Report

A 59-year-old man suffering from numbness of the left chin, pain behind the right eye, diplopia, and right ophthalmoptosis was admitted to our hospital. His symptoms had emerged successively and deteriorated rapidly starting approximately six weeks prior to being admitted. He had been in good health until then and had no particular past history of illness except mild hypertension. Ten days after the initiation of the above symptoms, he visited the departments of neurology and ophthalmology at our hospital where he was diagnosed with NCS and PO. A thorough investigation including magnetic resonance imaging (MRI) of the brain was performed; however, the causes of the NCS and PO could not be determined. Thereafter, his symptoms worsened, and a repeat MRI of the brain performed two weeks later re-
revealed the presence of a tumor in and around the cavernous sinus (Fig. 1a, c, d) as well as multiple bone lesions (Fig. 1b). In addition, systemic computed tomography (CT) revealed a retroperitoneal tumor around the prostate and urinary bladder. Lymph node swelling adjacent to this tumor contributed to the formation of a large mass (Fig. 2). A transrectal ultrasound-guided needle biopsy of the retroperitoneal tumor confirmed a diagnosis of diffuse large B-cell lymphoma, and he was admitted to our department in July 2012.

Upon admittance, his general condition was poor due to general malaise and the neurological symptoms described above. The patient had lost 7 kg in weight during the month before presentation. He was mentally alert and had stable vital signs, but he did present with a slight fever. A physical examination revealed no peripheral lymphadenopathy, hepatosplenomegaly or peripheral edema. He had double vision in all directions and bilateral ophthalmoptosis with right-sided predominance. The abduction of his right eye was completely restricted and movements in other directions were partially limited. The movement of his left eye was normal in all directions. The left side of the nasolabial sulcus was shallow with mild ptosis of the ipsilateral labial angle. There was a mild sensory disturbance at the left buccal, mental and nasal regions. No other neurological deficits were detected. A complete blood test revealed slight normocytic anemia (hemoglobin, 11.6 g/dL) and thrombocytopenia (platelet, 112,000/μL). The biochemical analyses revealed a significant elevation in serum lactate dehydrogenase (677 IU/L), C-reactive protein (7.72 mg/dL), ferritin (2,900 ng/mL), and soluble interleukin-2 receptor (4,790 U/mL). The levels of the other liver enzymes were within normal limits and renal function was normal. A thorough pathological investigation of the retroperitoneal tumor showed a diffuse growth pattern of large and atypical lymphoid cells (Fig. 3a, b) that were immunohistochemically positive for CD20 (Fig. 3c), CD79a (Fig. 3d), Bcl-2 and MUM-1. The cells were negative for CD5, CD10 (Fig. 3e) and Bcl-6 (Fig. 3f). In addition, the tumor had a minimal component focally showing an intravascular growth pattern (Fig. 3g, h). The Ki-67 index was high (>90%, Fig. 3i). A pathological diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified, was made and subclassified into the non-germinal center B-cell subtype according to Hans’ criteria (1). A biopsy of the prostate revealed a normal histology of prostate, so the tumor was not considered to be derived from the prostate. Bone marrow aspiration and biopsy revealed no apparent infiltration of lymphoma cells in the bone marrow. The clinical stage was identified as IV-B, and the patient was classified as being at high risk according to
the international prognostic index. CT revealed the retroperitoneal tumor to be the largest; therefore, it was considered to be the primary lesion. Positron emission tomography could not be performed due to the urgency of starting therapy following the confirmation of the diagnosis.

The patient’s clinical course is shown in Fig. 4. Immediately after the diagnosis was established, we performed a lumbar puncture and intrathecally administered methotrexate, cytarabine and dexamethasone. No lymphoma cells were detected in the cerebrospinal fluid. The patient realized some improvement in his ophthalmoplegia on the day after the intrathecal injection. Subsequently, we initiated the standard R-CHOP regimen consisting of rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin hydrochloride (50 mg/m^2), vincristine (2 mg/body) and prednisolone (100 mg/body for 5 days) without any major problems. Intrathecal chemotherapy was repeated four times during the first two courses of R-CHOP. Thereafter, we administered intravenous high-dose chemotherapy (R-MA) consisting of methotrexate (1 g/m^2), cytarabine (2 g/m^2 4 times at 12-h intervals) and rituximab (375 mg/m^2). The patient developed a febrile neutropenia which improved within one week following the administration of granulocyte colony stimulating factor (G-CSF) and antibiotics. The patient achieved complete response following a total of five courses of R-CHOP and three courses of R-MA (Fig. 5). His neurological deficits were resolved completely, including the diplopia and the ophthalmoptosis, although the numbness of the chin remained to some extent. Finally, as a consolidation therapy, high-dose chemotherapy (HDT) was performed followed by an autologous peripheral blood stem cell transplantation. The HDT consisted of ranimustine (300 mg/m^2 on day -7), etoposide (200 mg/m^2 on days -6 to -3), cytarabine (200 mg/m^2 twice daily on days -6 to -3) and melphalan (140 mg/m^2 on day -2). The stem cells were infused on Day 0. CD34-positive cells were infused at 2.1x10^6/kg. No major problems arose during the treatment except severe bone marrow suppression and febrile neutropenia. The febrile neutropenia was well controlled by the administration of G-CSF and antibiotics. Neutrophil engraftment was confirmed from Day 11 onward. Thereafter, he recovered well and has since been in good clinical condition.

**Discussion**

NCS is characterized by some type of sensory neuropathy including unilateral hypesthesia or paresthesia over the lower lip, chin, or gingiva. NCS is caused by various diseases and it is important to note that NCS can be a sign of malignancy in rare cases (2). There have been reports of cases in which NCS was a harbinger of malignant tumors such as breast cancer, non-Hodgkin’s lymphoma and acute lymphoblastic leukemia (3-5). Various mechanisms of NCS have been proposed, including the compression of the inferior alveolar or mental nerve at the mandible, the compression of the mandibular division of the trigeminal nerve at the skull base, or leptomeningeal tumor infiltration (2). PO is characterized by orbital pain plus ipsilateral ocular motor nerve palsies with or without oculosympathetic paralysis. Sensory loss can occur in the distribution of the ophthalmic nerve and occasionally in the maxillary division of the trigeminal nerve. PO is also caused by various diseases, including inflammatory diseases such as Tolosa-Hunt syndrome or sarcoidosis, vascular disorders, infectious diseases, and neoplasms such as metastatic cancer, meningioma or non-Hodgkin’s lymphoma (6).

Some important cranial nerve tracts such as the oculomotor, trochlear, trigeminal, and abducens nerves traverse the cavernous sinus and its vicinity, and tumors infiltrating this area may cause various neurological deficits including NCS and PO. However, such cases have only been reported sporadically in the literature. A few cases of non-Hodgkin’s lymphoma as a cause of NCS and PO have been reported in recent years, i.e., two cases of Burkitt’s leukemia/lymphoma (7, 8) and one case of DLBCL (9). The clinicopathological features of these cases are summarized in Table. Two of these cases were reported to have had cavernous sinus tumors (8, 9). In these cases and in the present case, lymphoma infiltration toward the cavernous sinus and the surrounding subarachnoid space is speculated to have disturbed the function of these cranial nerves, leading to the occurrence of NCS and PO, even though no lymphoma cells were detected in the cerebrospinal fluid. The serum levels of LDH and CRP were all elevated in the assessable cases, which might indicate the clinical aggressiveness of the ma-

**Figure 2.** Computed tomography of the primary retroperitoneal tumor at presentation showed a retroperitoneal tumor around the prostate and urinary bladder (arrow) which formed a mass in the cavity of the lesser pelvis.
Figure 3. Pathological findings. (a, b) Hematoxylin and Eosin staining showed a diffuse growth pattern of abnormal cells with the appearance of medium-to-large-sized lymphocytes. (c-f) An immunohistochemical study indicated that the lymphoma cells were positive for CD20 (c) and CD79a (d) but negative for CD10 (e) and Bcl-6 (f). (g, h) A focal intravascular growth pattern of the lymphoma cells was detected. (i) The Ki-67 labeling index of the lymphoma cells was judged to be > 90%.

Lignancy. Favorable clinical outcomes were achieved in all of the cases that were treated actively. However, not all of the neurological symptoms were resolved even in the cases which achieved remission as these symptoms could be indicative of permanent neurological damage.

It is unknown as to whether the complication of NCS and/or PO with a cavernous sinus tumor in a lymphoma patient will indicate a definite infiltration of lymphoma cells toward the CNS. It is possible that the symptoms are caused exclusively by the external compression of cranial nerves. In this case, however, the following points suggested that CNS infiltration was more likely. First, no cavernous sinus tumor was detectable by MRI at the initial presentation of NCS and PO, which suggests a leptomeningeal tumor progression. Second, a rapid amelioration of neurological symptoms was achieved after the first round of intrathecal chemotherapy, which was performed before the initiation of systemic chemotherapy. Third, a pathological examination revealed a component of lymphoma cells with an intravascular growth pattern. Considering the high frequency of CNS infiltration in intravascular large B-cell lymphoma cases (10), the intravascular components may have contributed to the tendency of CNS infiltration of lymphoma cells in this case. The CNS infiltration of lymphoma is of great clinical significance as the prognosis in these patients is poor in the absence of effective therapeutic strategies. Therefore, in order to avoid undesired outcomes, it is reasonable to consider such cases as having CNS infiltration and to treat with a regimen that can also target CNS lymphoma.

DLBCL patients with CNS infiltration have extremely poor survival rates, and there is no consensus concerning the best therapy for primary systemic DLBCL with CNS infiltration. Tomita et al. analyzed the clinical data from 1,221 primary systemic DLBCL patients and reported that the cumulative 5-year probability of CNS events was 8.4% and that the 2-year overall survival rate after a CNS event was only 27.1% (11). It has also been reported that a CNS relapse in systemic DLBCL has a poor outcome even after a high-dose chemotherapy including methotrexate (12, 13). At present, there are no promising and practical regimens for CNS lymphoma other than those containing high-dose methotrexate; thus, further investigations of new therapeutic strategies for such cases are required. In this case, we administered high-dose methotrexate and cytarabine with reference to the previous report of a R-hyperCVAD/MA regimen for lymphoma with CNS tropism (14). The therapeutic strategies described above were successful in this case; however, particular attention is needed regarding a CNS relapse.
of lymphoma.

In the rituximab era, the efficacy of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDT-ASCT) for the initial treatment of DLBCL remains to be determined. Some groups have reported a possible improvement in survival rates through the use of early HDT-ASCT in chemotherapy-sensitive patients with a high IPI risk (15). For the case presented herein, we decided to perform HDT-ASCT after taking the following points into consideration. First, the patient had a high IPI risk disease with an atypical extranodal presentation, so we speculated that his prognosis would be poor. Second, he was in a good general condition without any particular complications. Third, his disease was sensitive to chemotherapy and well-controlled with R-CHOP and R-MA.

In this case, the largest tumor was located in the retroperitoneal space and was separated from the pelvic organs, including the prostate and urinary bladder. Therefore, the di-
agnosia of primary retroperitoneal lymphoma was considered to be appropriate. Primary retroperitoneal DLBCL (PRLBCL) is a rare subtype of lymphoma with only sporadic cases reported in the literature, and the clinicopathological features of PRLBCL still remain to be elucidated. Pileri et al. analyzed the clinical and pathological findings of nine cases of PRLBCL (16), but could not find any characteristics specific to this disease entity. They suggested that PRLBCL could represent a heterogeneous group of tumors. To our knowledge, this is the first report of PRLBCL showing the clinicopathological features as described above.

In summary, we presented a case of primary retroperitoneal DLBCL with cavernous sinus infiltration that caused the NCS and PO which were the initial signs of lymphoma. Clinicians should consider the possibility of association with systemic lymphoma in cases of NCS or PO. Standard rituximab-containing chemotherapy combined with high-dose chemotherapy containing methotrexate is promising in such cases. However, special attention is required regarding a relapse of the disease.

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

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