Bilateral numb chin syndrome leading to a diagnosis of Burkitt’s cell acute lymphocytic leukemia: a case report and literature review

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Numb chin syndrome (NCS), also known as mental nerve neuropathy, is characterized by facial and oral numbness restricted to the distribution of the mental nerve. Although not a common neuropathy, the clinical importance of this syndrome lies in its frequent association with malignancies, particularly breast cancer and lymphoma. In this paper, we present a rare case of Burkitt cell acute lymphocytic leukemia initially presenting with bilateral NCS. In this case, no abnormalities were detected on initial blood tests and radiologic investigations except for partial loss of lamina dura around mandibular teeth. Furthermore, we found no evidence of any other signs of central nervous system involvement apart from NCS. Nevertheless, the patient continued to experience severe bilateral mandibular pain and paresthesia, prompting us to repeat the blood studies. These showed lymphomatous cells, yielding the diagnosis of leukemia 37 days after the original presentation. When a patient presents with the extremely unusual symptoms of bilateral numbness of lower lip and chin, we should suspect the presence of a malignancy even in the absence of any relevant past history. If the initial radiologic investigations and blood tests reveal no abnormalities, malignancy should not be removed from the differential diagnosis until a definite cause has been found. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e11-e16)

CASE REPORT

On June 6, 2000, a 48-year-old Japanese woman presented with bilateral numbness of the lower lip and chin and severe bilateral mandibular pain to the Department of Oral and Maxillofacial Surgery of the Tokai University School of Medicine. Her symptoms first appeared in early May, and 3 weeks after onset she underwent right lower second molar extraction by her dentist. This failed to improve her symptoms, and she was admitted for further investigation 9 days after the dental extraction. Her medical history was unremarkable; in particular, no history of trauma to the jaw was noted. On initial presentation there were no signs of fever, anemia, fatigue, headache, vomiting, or lymphadenopathy. There was no mandibular swelling, gingival enlargement, or gingival hemorrhage. She continued to experience severe bilateral mandibular pain. There were no abnormalities on neurologic examination except for hypoesthesia to thermal stimulation and pin prick over the distribution of the inferior alveolar and lingual nerves bilaterally. The peripheral full blood examination was normal. Pantomography showed partial lack of lamina dura bilaterally around the mandibular teeth (Fig. 1). Computer tomography (CT), magnetic resonance imaging (MRI), and nuclear bone scintigraphy (bone scan) revealed no mandibular lesions (Fig. 2). CT and MRI scans of the head showed no abnormalities.

The differential diagnosis at this stage was odontogenic infection, malignancy, and psychogenic disease. Differentiation between odontogenic infection and malignancy was difficult, so we commenced antibiotic treatment as a form of diagnostic therapy, with no improvement in her clinical condition. Consultation with our psychiatric colleagues failed to rule out psychogenic disease. On the seventh day of her admission, routine investigations revealed a markedly elevated lactate dehydrogenase level (4,683 IU/dL). Serum lev-
She then developed acute renal failure. At that point, we suspected a hematologic malignancy and referred her to our hematologist colleague. The peripheral blood white blood cell differential showed 1% lymphomatous cells, and bone marrow aspiration and biopsy revealed extensive infiltration by leukemic cells of the Burkitt type (Fig. 3). $^{67}$Ga scintigraphy revealed increased uptake in both breasts and ovaries (Fig. 4).

The final diagnosis was Burkitt cell acute lymphocytic leukemia. Acute renal failure was caused by acute spontaneous tumor lysis syndrome associated with this condition. Systemic treatment was commenced with diuretics, allopurinol, and alkalization. The patient also required hemodialysis because of the rapid deterioration of her renal function. After her recovery from acute renal failure, the patient underwent chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone, resulting in complete remission. She developed a transient oculomotor nerve palsy during chemotherapy, although cytologic analysis of the cerebrospinal fluid (CSF) was normal. At the time of writing, the patient remains alive with no evidence of recurrence 10 years after treatment.
DISCUSSION

Mental neuropathy associated with malignancy was first referred to as NCS in 1963 by Calverley and Mohanac, who reported 5 patients with metastatic malignant disease who initially presented with NCS. This syndrome has since been reported in various malignant diseases, including lymphoma, acute leukemia, Burkitt lymphoma/leukemia, multiple myeloma, Ewing sarcoma, melanoma, breast cancer, prostate cancer, lung cancer, colon cancer, and esophageal cancer. It is most commonly associated with breast cancer and lymphoma. NCS may be the first presentation of an underlying malignancy, and may also be the first sign of recurrence or metastasis in patients with a history of malignancy. Although not a common neuropathy, the clinical importance of this syndrome lies in its frequent association with malignant disease.

The mandibular nerve can be affected either intra- or extracranially. In cases of extracranial involvement, the most common etiology is involvement of the inferior alveolar nerve within the mandible. This can result from mechanical nerve compression caused by osseous involvement of the mandible or from nerve damage caused by tumor infiltration along the nerve sheath. In cases of intracranial involvement, the pathogenesis of NCS can be either involvement of the trigeminal nerve root by meningeal carcinomatosis or direct infiltration of malignant cells into the trigeminal nerve. Cases of intracranial involvement are often associated with other CNS signs, such as other cranial neuropathies, headache, or vomiting. In the present case, CT and MRI scans of the head and neck did not reveal any abnormalities, the bone scan was also normal, and cytologic analysis of the cerebrospinal fluid failed to reveal the presence of tumor cells. However, the presence of numbness of the lower lip and chin bilaterally, as well as the onset of oculomotor nerve palsy during chemotherapy, indicated that the responsible lesion for NCS in this case was likely to be intracranial.

On the other hand, this patient’s pantomograph revealed partial loss of lamina dura around the mandibular teeth. In another case with similar radiologic findings, a mandibular biopsy confirmed recurrence of acute leukemia. There may also have been infiltration of the mandible by tumor cells in our case. A study of the pantomographic findings in 214 children with acute leukemia stated that “alterations of the jaws, including a loss or thinning of the crypts in developing teeth, a loss or thinning of the lamina dura in erupted teeth, and a displacement of the teeth” were seen in 62.9% of cases. Another study of mandibular changes in 6 patients with hematologic disorders found that MRI signals in the bone marrow of the mandible had altered in all cases. However, in the present case, despite the use of pantomography, CT, MRI, and bone scanning, the responsible lesion for our patient’s NCS was not identified, although loss of lamina dura could be suggestive of the disease or other disorders (i.e., osteomyelitis, various systemic diseases).

In general, MRI is considered to be useful in the early diagnosis of cranial nerve involvement of hematologic malignancies. However, there have been several reports of MRI failing to detect the responsible lesion for NCS. A study of neurolymphomatosis associated with hematologic malignancies found that MRI was able to detect abnormalities in 77% of cases, and positron-emission tomography (PET) in 84%. A report of a case of NCS associated with Burkitt lymphoma stated that no abnormalities were seen on bone scan or MRI scans of brain and head, but PET scanning revealed hot spots in the mandible. When MRI scanning does not reveal any definite abnormalities, PET scanning may be advisable. There were only a few PET machines in Japan in 2000 when the present patient presented, so in this case we were unable to perform PET scanning. CSF cytology is estimated to have a >95% specificity for neoplastic meningitis, but it has a relatively low sensitivity (<50%), giving a high false negative rate. The sensitivity of CSF cytology is considered to increase with repeated testing. In 1 case of bilateral NCS associated with lymphoma, the initial MRI scan showed no abnormality, but a tumor in the cavernous sinus was detected on repeated MRI scanning 2 months later. In another case of lymphoma-related NCS, the initial bone scan was clear, but abnormalities were detected on a further bone scan 3 months later. Repetition of radiologic investigations may also increase their detection rates.

Bilateral numbness of the lower lip and chin is extremely unusual. Our search of the literature revealed 22 cases of bilateral NCS associated with malignancy (Table I). The primary disease was lymphoma in 7 cases, Burkitt lymphoma/leukemia in 5, breast cancer in 3, prostate cancer in 3, and other malignancy in 4. There were 15 cases with hematologic malignancies, and 7 with solid malignancies. The onset of bilateral NCS preceded the diagnosis of the primary tumor in 8 out of the 22 cases. In the remaining 14 cases, the primary tumor had already been diagnosed, and the onset of NCS was associated with progression, recurrence, or metastasis of the primary tumor. According to our review of the literature, more cases of bilateral NCS are associated with hematologic malignancies than with solid malignancies. The incidence of meningeal carcinomatosis in breast cancer patients is of the order of 1%-2%. On the other hand, 1 study found lymphomatous involvement of the CNS in 5% of pa-
tients with non-Hodgkin lymphoma.\textsuperscript{42} Reported CNS relapse rates for patients with acute lymphoblastic leukemia, lymphoblastic leukemia, and Burkitt lymphoma are 30\%-50\%.\textsuperscript{43} Hematologic malignancies infiltrate the CNS more readily than solid malignancies, possibly accounting for the high proportion of bilateral NCS. In general, it is extremely unusual for metastases from a solid malignancy to involve the extracranial portion of the mandibular nerve bilaterally at the same time. Our search of the literature revealed only 2 such cases of bilateral NCS involving this mechanism, one of prostate carcinoma metastases to both sides of the mandible, reported by Requena et al.,\textsuperscript{17} and another of bilateral NCS associated with breast cancer reported by Bruyn and Boogerd.\textsuperscript{7}

Of the cases we reviewed, the onset of bilateral NCS preceded the diagnosis of the primary tumor in 8 out of the 22 cases (Table II). In 5 of the 6 case studies with records of imaging results, there were abnormal radiologic findings. Other cranial neuropathies were present in 4 out of 8 cases. Oromaxillofacial symptoms other than NCS, toothache and mandibular pain, were reported in 4 out of 8 cases, including in the present case. Although they are not specific to malignancy, perhaps dentists should take special heed of these symptoms. In our case, there were no abnormalities except for loss of lamina dura seen on imaging of the head and neck region, no neurologic abnormalities other than NCS, and no abnormalities on the initial blood tests. Consultation with our psychiatric colleagues failed to rule out psychogenic disease. From the above results, with our patient complaining of severe pain, we included psychogenic disease in the differential diagnosis. It is important to note that no abnormalities were seen on her blood tests at the time of initial presentation, although abnormalities had developed 7 days later. Despite the lack of abnormalities on the initial blood tests, we did not exclude malignancy from the differential diagnosis, and we continued to monitor our patient closely until blood tests provided the diagnosis 1 week later. We were able to identify 2 earlier reports of cases in which, as in our case, initial blood tests were negative but later blood tests revealed a hematologic malignancy.\textsuperscript{44} These 3 cases, including ours, suggest the possibility of conversion of blood tests over a period of several days to several weeks, and the advisability of repeating blood tests in a patient with persistent paresthesia. Thus, when a patient presents with the extremely unusual symptoms of bilateral numbness of lower lip and chin, even if they have no history of malignancy, we

\begin{table}[h]
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\begin{tabular}{|l|c|c|c|}
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\textbf{Author} & \textbf{Patient age/gender} & \textbf{Primary disease} & \textbf{Timing of NCS} \\
\hline
1 & Sweet\textsuperscript{55} & 33/F & Burkitt lymphoma/leukemia & PD \\
2 & Hiraki\textsuperscript{10} & 15/M & Burkitt lymphoma/leukemia & PD \\
3 & Kuroda\textsuperscript{12} & 57/M & Burkitt lymphoma/leukemia & PD \\
4 & Milani\textsuperscript{13} & 33/F & Burkitt lymphoma/leukemia & PD \\
5 & Mizutani\textsuperscript{14} & 55/M & Lymphoma & PD \\
6 & Ohno\textsuperscript{15} & 32/F & Acute monoblastic leukemia & PD \\
7 & Shiroshita\textsuperscript{14} & 73/M & Multiple myeloma & PD \\
8 & Requena\textsuperscript{17} & 78/M & Prostate cancer & PD \\
9 & Ojaguren\textsuperscript{36} & 57/M & Lymphoma & R or DP \\
10 & Barrett\textsuperscript{37} & 46/M & Lymphoma & R or DP \\
11 & Barrett\textsuperscript{37} & 45/M & Lymphoma & R or DP \\
12 & Nobler\textsuperscript{38} & 39/M & Lymphoma & R or DP \\
13 & Nobler\textsuperscript{38} & 45/M & Lymphoma & R or DP \\
14 & Rubinstein\textsuperscript{39} & 35/F & Lymphoma & R or DP \\
15 & Bruyn\textsuperscript{7} & 17/F & Burkitt lymphoma & R or DP \\
16 & Barrett\textsuperscript{37} & 28/M & Acute lymphocytic leukemia & R or DP \\
17 & Laurencet\textsuperscript{2} & 77/F & Breast cancer & R or DP \\
18 & Bruyn\textsuperscript{7} & 54/F & Breast cancer & R or DP \\
19 & Bruyn\textsuperscript{7} & 72/F & Breast cancer & R or DP \\
20 & Mohammed\textsuperscript{18} & 62/M & Prostate cancer & R or DP \\
21 & Laurencet\textsuperscript{2} & 47/M & Prostate cancer & R or DP \\
22 & Rubinstein\textsuperscript{39} & 15/M & Neuroblastoma & R or DP \\
23 & Present patient & 48/F & Burkitt lymphoma/leukemia & PD \\
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\end{tabular}
\caption{Bilateral numb chin syndrome (NCS): a review of the literature}
\end{table}

PD, Previous diagnosis of primary disease; R or DP, recurrence or disease progression of primary disease.
should suspect the presence of a malignancy. Even if the initial radiological investigations and blood tests reveal no abnormalities, malignancy should not be removed from the differential diagnosis until a definite cause has been found.

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