

Case Study

# Diffuse Large B-Cell Lymphoma with Mass Lesions of Skull Vault and Ileocecum

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We report a rare case of non-Hodgkin lymphoma with mass lesions of skull vault and ileocecum. The patient was an 82-year-old Japanese woman who exhibited a painless subcutaneous scalp tumor in the right parietal region associated with no neurological abnormalities. Magnetic resonance imaging of the head demonstrated a mass in the skull vault with iso- to hypointense signals on both T1- and T2-weighted imaging. Biopsy of the mass revealed that the tumor comprised large cells that were immunoreactive for CD20 (L-26) and CD79a. Diffuse large B-cell lymphoma (DLBCL) was therefore diagnosed. Further investigation could not identify any other evidence of systemic lymphoma other than ileocecal lesions. She was treated by irradiation (45 Gy) of the mass on the parietal bone and with rituximab, pirarubicin, cyclophosphamide, and vincristine. The patient achieved complete remission after 3 cycles of systemic chemotherapy. As of 30 months after presentation, no signs of lymphoma have been found. [*J Clin Exp Hematop* 53(3) : 215-219, 2013]

**Keywords:** cranial vault lymphoma, colonic lymphoma, diffuse large B-cell lymphoma, radiation, chemotherapy

## INTRODUCTION

The involvement of bone in disseminated non-Hodgkin lymphoma (NHL) is not uncommon, occurring in up to 25% of patients.<sup>1,2</sup> Primary involvement of the bone is extremely rare in Hodgkin lymphoma, whereas NHL arises from a skeletal location in up to 4% of cases, particularly in the long bones of the upper and lower extremities, the pelvis, and the spine.<sup>1,2</sup> Initial involvement of the skull at presentation is extremely rare and primary cranial vault lymphoma constitutes only 0.2% of lymphoma cases.<sup>3</sup> No consensus has been reached regarding the treatment for lymphoma of the skull.

We here discuss the biological characteristics and treatment of our case compared with previously reported cases of solitary skull vault lymphoma.

## CASE REPORT

An 82-year-old Japanese woman visited hospital with a painless subcutaneous scalp tumor on the parietal region. Performance status was 0 according to the Eastern Cooperative Oncology Group.<sup>4</sup> The patient had a past history of chronic hepatitis C, but anti-human immunodeficiency virus antibody was negative. There were no episodes of head injury before the emergence of the subcutaneous scalp mass. Physical examination revealed a firm nonpulsatile and immovable subcutaneous mass measuring 3.0 × 3.0 cm in the right parietal area. She was afebrile, with no lymphadenopathy or hepatosplenomegaly. Magnetic resonance imaging (MRI) of the head demonstrated a solitary mass of the skull vault with iso- to hypointense signals on both T1- and T2-weighted imaging (Fig. 1). The center of the mass was located within diploe and projected into inner and outer tables. The skull was completely destroyed and the tumor was adjacent to the dura.

Biopsy of the subcutaneous scalp mass showed that the tumor comprised large cells that were immunoreactive for CD20 (L-26) (Figs. 2 & 3) and CD79a, but not CD3, CD5, bcl-2, or *in situ* hybridization for Epstein-Barr virus-encoded RNA (EBER)-1, indicating diffuse large B-cell lymphoma

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Received : May 12, 2013

Revised : July 6, 2013

Accepted : July 29, 2013

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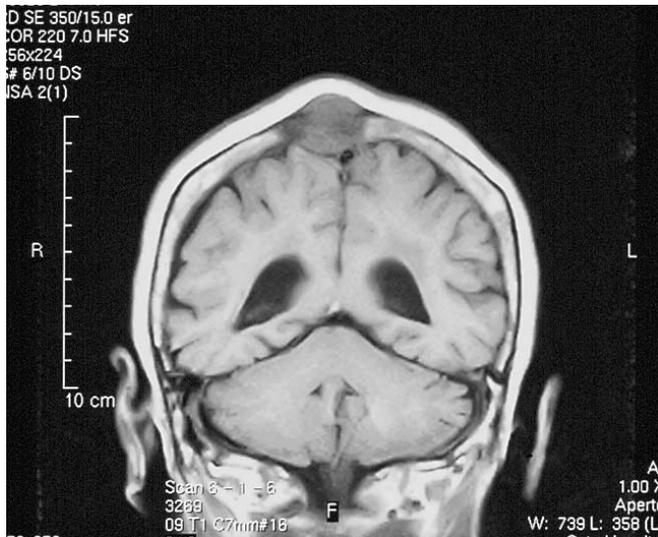
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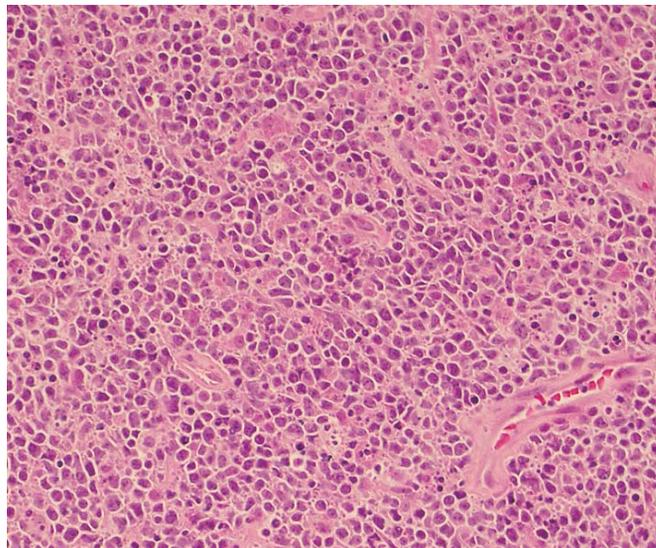
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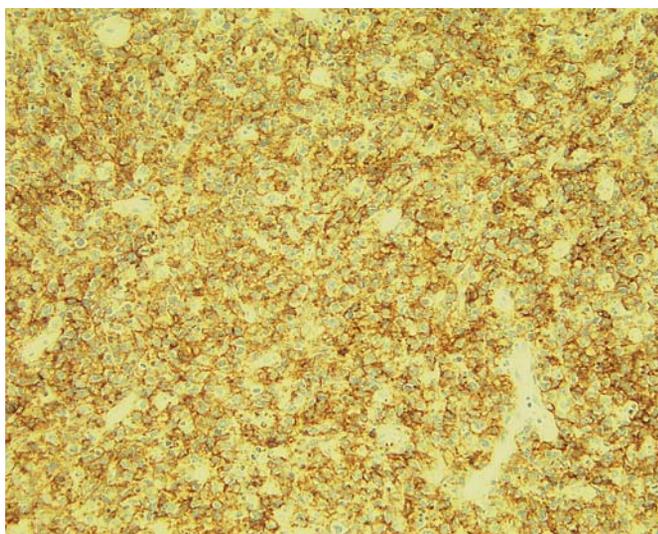
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**Fig. 1.** Magnetic resonance imaging of the head demonstrating a solitary mass of the cranial vault with signal hypointensity on T1-weighted imaging.



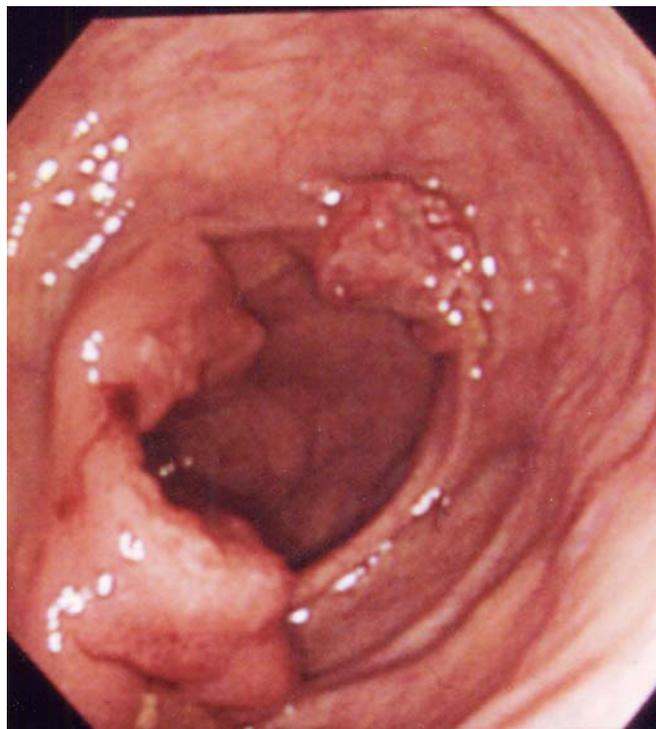
**Fig. 2.** Histological features showing that the tumor comprises large cells. H&E stain,  $\times 200$ .



**Fig. 3.** Histological examination showing that the large tumor cells are immunoreactive for CD20 (L-26) ( $\times 200$ ).

(DLBCL). MIB-1 index was 72.8%.

The patient was admitted to our hospital. Hematological examination on admission showed a white blood cell count of  $5,460/\text{mm}^3$  with a normal differential, hemoglobin level of 10.0 g/dL, and platelet count of  $139,000/\text{mm}^3$ . Blood biochemistry was unremarkable. Serological examination showed elevated soluble interleukin-2 receptor (1,093 U/mL). Bone marrow aspiration and biopsy from the posterior iliac spine revealed no marrow involvement. Cerebrospinal fluid cytology was negative for lymphoma cells. Contrast-



**Fig. 4.** Total colonoscopy demonstrating mass lesions in the ileocecum.

enhanced computed tomography of the neck, chest, abdomen, and pelvis showed no evidence of lymphoma lesions. Bone scintigraphy revealed no abnormal uptake other than in the parietal bone lesion. However, while upper gastrointestinal endoscopy revealed no lymphoma lesion, total colonoscopy

demonstrated mass lesions at the ileocecum (Fig. 4) and a biopsy was taken, which confirmed the diagnosis of DLBCL. The tumor cells were immunoreactive for CD20 (L-26) and CD79a, but not CD3 and bcl-2. The ileocecal mass was smaller than the subcutaneous scalp mass.

The patient was referred to our hospital for radio- and chemotherapy. The skull vault lymphoma was treated first because ileus due to ileocecal mass lesions was considered unlikely. Whole brain was irradiated with 34.2 Gy in 17 fractions, involving field irradiation with 10.8 Gy in 6 fractions over 36 days. A few days after irradiation, the subcutaneous scalp tumor was not palpable. After completion of radiotherapy, the patient was treated with systemic chemotherapy. She was administered 500 mg of rituximab on day 1, and then 40 mg of pirarubicin, 700 mg of cyclophosphamide, and 1.4 mg of vincristine on day 2. As she had a past history of chronic hepatitis C, prednisolone was not used. Systemic chemotherapy was interrupted by severe myelosuppression after the completion of 3 cycles. Tumor regression of ileocecal lesions was confirmed by total colonoscopy after 3 cycles of systemic chemotherapy. As of 30 months after presentation, no signs of lymphoma have been found.

## DISCUSSION

Primary bony Hodgkin lymphoma is extremely rare, and NHL originating primarily in bone is seen in only about 4% of patients. Bone involvement is typically seen in the femur, tibia, pelvis, spine, mandible, and scapula.<sup>1,2</sup> Skull vault lymphoma is different from bony lymphoma of other sites because treatment of the central nervous system (CNS) is required in cases with the involvement of cerebral structures by direct invasion. True primary malignant lymphoma of the bone is defined as a solitary mass lesion without any evidence of disease at another site and no systemic dissemination within 6 months of tumor detection.<sup>5,6</sup> The present case thus does not fulfill the criteria for primary malignant lymphoma of the bone owing to the presence of colon lesions.

We compared the immunohistochemical data of ileocecal lymphoma to those of skull vault lymphoma; however, there were no obvious differences between the two lesions. There has been a case report of concurrent adenocarcinoma and DLBCL in the colon, which first presented with DLBCL in the skull base and ileocecal junction area.<sup>7</sup> The collision tumors were associated with Epstein-Barr virus infection. In this case, EBER-1 *in situ* hybridization of skull vault lymphoma was negative; however, that of ileocecal lymphoma could not be carried out. Although we attempted to analyze the mutation status of the *IGH* gene of both mass lesions by polymerase chain reaction (PCR), PCR products of ileocecal lesions were not obtained, so it remains to be determined whether the two lesions have the same clonality. From the results of clinical examination, and immunohistochemical and

molecular analyses, we considered that it was difficult to discuss the possibility of systemic lymphoma in this case.

Primary cranial vault lymphomas have been reported in immunocompromised or trauma patients.<sup>8,9</sup> However, primary NHL of the skull with extra- and intracranial extension without systemic or skeletal manifestation in a non-immunocompromised and non-trauma patient is extremely rare. We found only 19 cases in the literature (Table 1).<sup>10-28</sup> Such cases of cranial vault lymphoma with systemic involvement, short observation, secondary involvement of the CNS including intra-axial lesions, progressive disease within 6 months, and multifocal primary cranial vault lymphoma are not included in Table 1. Only 1 case is included from the previous report of cranial vault lymphoma in which total colonoscopy was performed.<sup>11</sup>

The initial symptoms and signs of lymphoma in the skull include a painless scalp lump, headache due to bone destruction or tumor infiltration of meninges, seizures, and focal neurologic deficits secondary to neoplastic infiltration of the cerebral cortex. Lymphoma cells have been suggested to infiltrate the spaces within the diploe and extend along the emissary veins to infiltrate the soft tissues on either side of the bone.<sup>11</sup> Malignant lymphoma originating from the skull may extend outside the skull with bony changes at first, followed by infiltration and complete destruction of the skull.<sup>21</sup> In the present case, the skull was completely destroyed and tumor was adjacent to the dura. The dura has been reported to display strong resistance to lymphoma infiltration of the cerebral cortex.<sup>21</sup> In this case, there were no focal neurological deficits and cerebrospinal fluid cytology was negative for lymphoma cells. No obvious CNS involvement was identified.

MRI of the tumor in the present case showed iso- to hypointense signal intensity on both T1- and T2-weighted imaging. The MRI features of the present case were similar to previously reported cases.<sup>16,20,21</sup> With gadolinium-DTPA (diethylenetriaminepentacetate) administration, many cranial vault lymphomas displayed homogeneous findings.<sup>16,21</sup> As the appearance resembles that in metastatic carcinoma, osteomyelitis, or meningioma, histopathological examination is necessary to reach a definitive diagnosis.<sup>29</sup>

Optimum treatment for malignant lymphoma of the skull vault has not been established. Surgical removal followed by radio- and chemotherapy has been recommended.<sup>16,17</sup> In the present case, taking into consideration the age and absence of focal neurological deficits, we decided to use radiotherapy instead of surgical removal of the tumor from parietal bone. Clinical observations of the present case suggest that skull vault lymphoma without obvious CNS involvement, unlike primary CNS lymphoma,<sup>30</sup> does not always require intensive chemo-radiotherapy including intrathecal administration of cytotoxic agents or high-dose methotrexate/cytarabine (Ara-C).

**Table 1.** Clinical data and results of 19 patients with primary cranial vault lymphoma involving the skull

Case no.	Authors, Year, (Reference)	Age/ Sex	Initial symptom	Location	Management	Histology	Follow up and outcome
1	Agbi CB, <i>et al.</i> , 1983 [10]	58/F	Confusion, headache, focal deficit	Right parietal	Surgery	Cleaved cell lymphoma	Disease-free at 7 mon
2	Holtás S, <i>et al.</i> , 1985 [11]	60/F	Subcutaneous mass on the scalp	Left frontal	Steroid	Undifferentiated large cell malignant lymphoma of histiocytic type	Disease-free at 6 mon
3	Maiuri F, <i>et al.</i> , 1987 [12]	51/F	Headache, transient diplopia	Right parieto-occipital	Surgery and radiotherapy with 4,500 rads	Lymphoblastic lymphoma	Disease-free at 24 mon
4	Howat AJ, <i>et al.</i> , 1987 [13]	3/M	Not reported	Left frontal	Whole-cranium radiotherapy (24 Gy) and chemotherapy	Mixed large and medium-sized cell, some with cleaved nuclei	Alive at 133 mon
5	Kawakami K, <i>et al.</i> , 1988 [14]	52/F	Parietal scalp mass	Left parietal	Surgery and radiotherapy with <sup>60</sup> Co 4,500 rads	NHL (diffuse medium sized type)	Disease-free at 6 yr
6	Parekh HC, <i>et al.</i> , 1993 [15]	65/F	Headache, confusion, hemiparesis	Left parietal	Surgery and whole brain irradiation	Malignant non-Hodgkin's B-cell lymphoma	6 yr follow up ; died of unrelated cause
7	Sato M, <i>et al.</i> , 1993 [16]	65/F	Hemiparesis, parietal scalp mass	Right fronto-parietal	Surgery, radiation (50 Gy) and chemotherapy (THP-COP)	Malignant lymphoma, B cell type, diffuse large cell type	Disease-free at 20 mon after surgery
8	Isla A, <i>et al.</i> , 1996 [17]	75/F	Seizure	Left frontal	Surgery (excision) and radiation (45 Gy) and chemotherapy (VCR+cisplatin+DXR+PSL)	Low grade B-cell lymphoma centroblastic-centrocytic type with follicular pattern	Disease-free at 3 yr
9	Muin IA, <i>et al.</i> , 1997 [18]	60/M	Headache, confusion, forgetfulness, hemiparesis	Right parietal	Surgery, external beam radiotherapy and chemotherapy (CHOP)	High grade non-Hodgkin B-cell lymphoma	Recurrence-free at 8 mon
10	Jamjoom AB, <i>et al.</i> , 1998 [19]	25/M	Scalp mass, headache	Parietal	Surgery and radiotherapy (5,000 cGy)	Malignant lymphoma, large T-cell immunoblastic type	Disease-free at 5 mon
11	Duyndam DA, <i>et al.</i> , 2002 [20]	71/F	Scalp mass	Left frontal	Chemotherapy (chlorambucil 8 mg/day and PSL 20 mg/day) for 6 mon	Malignant non-Hodgkin lymphoma of the B-cell type	Disease-free at 2 yr
12	Kanai M, <i>et al.</i> , 2003 [21]	71/F	Scalp mass	Left fronto-parietal	Surgery and chemotherapy (3 cycles of THP-COP)	Diffuse, medium-sized, B cell lymphoma	Died at 3.5 yr
13	Mongia S, <i>et al.</i> , 2003 [22]	25/M	Scalp mass	Right fronto-temporo-parietal	Radiotherapy along with adjuvant chemotherapy	Non Hodgkin's lymphoma	Disease-free at 2.5 yr
14	Fukushima Y, <i>et al.</i> , 2007 [23]	60/F	Scalp mass	Right parietal	Surgery, local radiotherapy (50 Gy) and chemotherapy (CHOP)	Non Hodgkin's lymphoma of the diffuse, medium-sized, clear, B-cell type	Disease-free at 3 yr
15	Gaitonde S, <i>et al.</i> , 2008 [24]	70/F	Forehead mass	Right frontal	Surgery and localized radiation therapy	Follicular lymphoma, Grade 2	Relapsed at 9 mon after initial therapy
16	González-Bonet CG, <i>et al.</i> , 2008 [25]	84/F	Ictus	Right fronto-parietal	Surgery	Immunoblastic B-cell lymphoma	Disease-free at 5 mon after surgery
17	Renard D, <i>et al.</i> , 2009 [26]	67/F	Painful right-sided swelling	Right frontal	Chemotherapy (Rituximab+CHOP)	Diffuse large B-cell lymphoma	Not available
18	Fadouhair Z, <i>et al.</i> , 2011 [27]	42/F	Enlarging mass involving right parietal bone	Right parietal	Chemotherapy (4 cycles of Rituximab+CHOP) followed by involved field radiation	Diffuse large B-cell lymphoma	Disease-free at more than 9 mon after treatment
19	Martin J, <i>et al.</i> , 2012 [28]	50/M	Diffuse swelling in the left side scalp	Left parietal and occipital	Chemotherapy (6 cycles of CHOP)+local adjuvant external beam radiotherapy (36 Gy)	Diffuse primary cutaneous B-cell lymphoma	Not available

NHL, non-Hodgkin lymphoma ; MTX, methotrexate ; THP, pirarubicin ; COP, cyclophosphamide, vincristine and prednisolone ; VCR, vincristine ; DXR, doxorubicin ; PSL, prednisolone ; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone

The prognosis of malignant lymphoma appearing in the skull vault is unknown, but any involvement of cerebral structures by direct invasion or by leptomeningeal seeding and systemic involvement suggests an unfavorable prognosis. A thorough search is necessary to decide upon the treatment for lymphoma. Further accumulation of data for skull vault lymphoma is needed to improve the treatment and prognosis.

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