***De novo* CD5-positive Diffuse Large B-cell Lymphoma of the Temporal Bone Presenting with an External Auditory Canal Tumor**

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Abstract

We report a 74-year-old woman with primary CD5-positive diffuse large B-cell lymphoma (DLBCL) of the temporal bone. The patient was admitted because of a mass in the left external auditory canal. She was treated with eight courses of CEOP therapy (rituximab was added from the sixth course) followed by radiotherapy of 40 Gy, and complete remission was achieved. The occurrence of malignant lymphoma in the temporal bone, which is an extremely unusual site, may have depended on the peculiarity of CD5-positive DLBCL.

Key words: primary lymphoma of bone (PLB), temporal bone, external auditory canal, diffuse large B-cell lymphoma (DLBCL), CD5

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Introduction

Primary lymphoma of bone (PLB) is a rare disease that accounts for 1-2% of all malignant lymphoma and 3-5% of all extranodal lymphoma (1), and initial involvement of the temporal bone is even rarer. The most common sites involved in PLB are the extremities, particularly the femur (1-3). Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma, representing 30-40% of adult cases, and is regarded as a heterogeneous group of lymphoma in surface markers, histology, and clinical features (4, 5).

CD5 is a cell surface molecule expressed on most T cells and a subset of B cells. Among B-cell malignancies, CD5 is mainly expressed in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). Recently, CD5-positive DLBCL with no past history of lymphoproliferative disorder (*de novo* CD5⁺DLBCL) is regarded as a distinct subtype of DLBCL (6-8). *De novo* CD5⁺DLBCL, accounting for approximately 10% of DLBCLs, is characterized by elderly onset, female predominance, frequent involvement of a variety of extranodal sites, frequent association of international

prognostic index (IPI) (9), and aggressive clinical course (6). Here, we describe a case of primary CD5⁺DLBCL of the temporal bone with an external auditory canal mass and review the literature.

Case Report

A 74-year-old Japanese woman was referred to our hospital because of a left external auditory canal mass in June 2003. Six months before admission she complained of left ear fullness, and she was treated as left otitis media. The disease did not respond to treatment and swelling developed in the left external auditory canal. She had no history of lymphoproliferative disorder.

On admission, the patient was fully conscious and her performance status (PS) was 0. Her temperature was 37.4°C. On physical examination she showed slight swelling without tenderness in the left temporal region. Superficial lymph nodes were not palpable, and no abnormal findings were seen in either the chest or abdomen except for the presence of a systolic ejection murmur on cardiac auscultation. There were no abnormal findings on neurological examinations. She had no B symptoms (fever, night sweats and weight

Figure 1. A) Soft tissue window CT showed an enhanced mass in the left temporal muscle, the lateral pterygoid muscle, the middle fossa, the mastoid air cells, and the middle ear (arrows). B) Axial T2-weighted MRI showed a mass (arrows) destroying the left temporal bone, with involvement of the overlying temporal muscle, subcutaneous tissue, and subdural space.

loss) according to the Ann Arbor classification.

Laboratory studies on admission showed a red blood cell count of $349 \times 10^4/\text{mm}^3$, hemoglobin level of 10.2 g/dl, hematocrit of 30.6%, white blood cell count of $4,390/\text{mm}^3$, and platelet count of $22.4 \times 10^4/\text{mm}^3$. Serum lactate dehydrogenase (LDH) level was 226 IU/ml, and was within normal limits (normal range, 100-230 IU/ml). C-reactive protein (CRP) was 0.46 mg/dl (normal value less than 0.30 mg/dl). Soluble interleukin 2 receptor (sIL-2R) was slightly increased to 613.2 U/ml (normal range, 145.0-518.0 U/ml). Both anti-hepatitis C virus antibody and anti-human immunodeficiency virus antibody were negative. Serum Epstein-Barr virus (EBV)-specific antibodies suggested past infection. A bone marrow aspiration and biopsy showed hypocel-

Figure 2. Otoscopic examination revealed a soft mass from the upper wall of the left external auditory canal.

lular bone marrow without atypical cells infiltration. Cerebrospinal fluid examination, and lung and abdominal computed tomography (CT) scans were normal.

CT scanning of the head showed an enhanced mass spreading through both sides of the left temporal bone with involvement of the mastoid air cells and the middle ear (Fig. 1A). ^{67}Ga scintigraphy showed increased uptake only in the left temporal region. Magnetic resonance imaging (MRI) of the head revealed a mass destroying the left temporal bone, with involvement of the overlying temporal muscle, subcutaneous tissue, lateral pterygoid muscle, and subdural space. The mass lesion showed low signal intensity on T1-weighted images, and high irregular signal intensity on T2-weighted images (Fig. 1B).

An audiogram revealed a combined hearing loss in the left ear and a perceptible hearing loss in the right ear. Otoscopic examination revealed a soft pink to white mass with a smooth outer surface from the upper wall that was obstructing the left external auditory canal (Fig. 2). The tympanic membrane was normal. Biopsy specimens of the mass showed diffuse proliferation of abnormal large lymphoid cells (Fig. 3A). Immunohistochemical staining using frozen sections showed that the lymphoma cells were positive for CD5, CD20, CD21, and negative for CD3, CD10, CD23, BCL2, and cyclin D1 (Fig. 3BCD). Tumor cells expressed surface Ig G- κ .

She was diagnosed as having primary CD5⁺DLBCL of the temporal bone at clinical stage I EA with low-risk category of IPI (9). She was treated with CEOP chemotherapy consisting of cyclophosphamide at 750 mg/m^2 on day 1, epirubicin at 50 mg/m^2 on day 1, vincristine at 1.4 mg/m^2 on day 1, and prednisolone at 100 mg/body on days 1-5. From the sixth course, rituximab was added on day 1 of CEOP. She was discharged in October 2003 and treated as an outpatient from the seventh course. After eight courses of chemotherapy, she was treated with local radiotherapy of 40 Gy and

Figure 3. Histology of the tumor from the left external auditory canal. A) Diffuse infiltration of large-sized lymphoid cells was shown (Hematoxylin-eosin (HE) stain, $\times 200$). B), C), D) Tumor cells were positive for CD5 and CD20, and negative for CD3 ($\times 200$).

Table 1. Summary of Primary Lymphoma of the Temporal Bone

Case No.	Age (year)	Sex	Histology	Immuno-phenotype	Initial symptom	Therapy	Outcome	Reference
1	6	M	lymphocytic	-	otorrhea, mass from the external canal	S	Relapse, lost	13
2	66	M	lymphocytic	-	otalgia	CT	Dead	14
3	32	F	nodular, histiocytic	-	ear fullness, tinnitus, hearing loss	S, RT, CT	Dead	15
4	7	M	Burkitt's	-	swelling behind the ear	CT	Dead	16
5	6	M	Burkitt's	B	otalgia, low grade fever, loss of balance	S, CT	Alive	17
6	66	M	diffuse large cell	B	hearing loss, otalgia	S, CT RT	Dead	18
7	5	M	diffuse large cell	B	otalgia, otorrhea	CT	Alive	18
8	55	M	pleomorphic	T	ear fullness	RT, CT	Dead	19
9	40	M	diffuse small	B	convulsive attack	RT, CT	Alive	20
10	2	M	EBV+, high-grade B-cell lymphoma	B	otitis media, facial palsy	S, CT	Alive	21
11	78	M	large cell	-	mass in the temporal region	S, RT, CT	ND	22
12	66	F	diffuse large cell, immunoblastic	B	ear fullness	RT	Dead	23
13	16	M	large cell, immunoblastic	T	pain in the skull, facial palsy	CT, RT	Dead	24
14	75	M	large cell	B	otalgia, otorrhea, hearing loss	CT, RT	Alive	25
15	5	M	lymphoblastic	B	facial palsy, hearing loss	CT	Alive	26
16	15	M	diffuse histiocytic large cell	-	retroauricular mass	CT	Alive	27
17	81	F	DLBCL	B	abducens palsy, headache	CT, RT	ND	28
18	74	F	DLBCL	B	ear fullness	CT, RT	Alive	Present case

S: surgery, CT: chemotherapy, RT: radiotherapy, ND: not described

achieved complete remission. She is alive and well without any therapy 33 months after the diagnosis.

Discussion

PLB is a rare disease accounting for 1-2% of all malignant lymphoma and 3-5% of all extranodal lymphoma (1). The diagnostic criteria for PLB have been developed from those enumerated by Coley et al in 1950 and are as follows: 1) clinically a primary focus in a single bone on admission, 2) unequivocal histologic proof from the bone lesion, 3) metastases present on admission only if regional, or if the onset of symptoms of the primary tumor preceded the appearance of the metastases by at least six months (10). Currently, the criteria adopted by the World Health Organization are the

following: 1) a single skeletal site, with or without regional lymph node involvement; 2) multiple bones are involved, but there is no visceral or lymph node involvement (11).

PLB may occur in patients of any age group but has a tendency of adult onset and a male predominance (male-to-female ratio ranges from 1.5-2: 1) (2, 3, 11). The most common initial symptom is localized pain, and patients sometimes present with a palpable mass (1-3, 10). Patients rarely present with systemic symptoms, such as fever or night sweating (1, 2, 11). On conventional X-ray, PLB shows lytic, sclerotic, permeative lesions, or a combination of these (1). CT and MRI are useful for the diagnosis of PLB. However, on follow-up examinations, MRI is not useful to differentiate between persistent disease and healing bone (3). Positron emission tomography with fluorine 18-

fluorodeoxyglucose (FDG-PET) may be preferable for the assessment of remission status. Histopathologically, PLB is usually diagnosed as DLBCL (1-3, 10, 11). It is considered that PLB usually requires radiotherapy with chemotherapy (3). Generally, the prognosis of PLB is favorable, and the 5-year overall survival is approximately 60% (2, 11, 12).

The most common sites involved in PLB are the extremities, particularly the femur (1-3), and initial involvement of the temporal bone is extremely rare. We found only 17 reported cases of primary temporal bone lymphoma in the English and Japanese literature, including the cases of primary lymphoma of the middle ear (13-28). A total of 18 cases (14 patients males, and 4 females), including the present case, are summarized in Table 1. The age at diagnosis ranged from 2 to 81 years with a tendency to involve children and elderly ages. The most common initial symptoms were ear symptoms (12 of 18) such as otalgia, hearing loss, and ear fullness. Some patients presented with facial nerve palsy (3 of 18), or localized swelling (3 of 18). The temporal bone contains the sensory organs of hearing and balance (the inner ear, the middle ear, and the external auditory canal), and the facial nerve passes through the temporal bone. The symptoms of temporal bone lymphoma, such as ear symptoms and facial nerve palsy, are related to these anatomical features. On otoscopic examination, 5 patients, including our case, had a soft mass in the external auditory canal (13, 15, 20, 23). Immunophenotypic analysis was performed in 12 patients, and 10 out of 12 patients were B-cell type. The expression of CD5 was not examined in any previously reported case. Among 18 cases, 8 patients were alive, and 7 were dead, and it suggests that primary temporal bone lymphoma seems to be similar in prognosis to PLB.

On the other hand, there have been only 3 reported cases

of primary lymphoma of the external auditory canal (29-31), and there was no bone destruction in these cases. Interestingly, 2 of 3 patients had bilateral tumors (29, 30) and one of these involved the use of hearing aids for a long period of time (29). There has been one other report of malignant lymphoma of the external auditory canal in a human immunodeficiency virus (HIV)-positive patient, but this originated in the infratemporal fossa and grew through the eustachian tube to present in the ear canal (32). Primary lymphoma of the inner ear is also extremely rare (33). Although biopsy of the bone lesion was not performed in our case, we considered the disease as primary temporal bone lymphoma based on CT and MRI findings that showed the mass lesion destroying the bone and spreading through both sides of the bone. However, it was not clear whether the primary site of the disease was the temporal bone or adjacent soft tissue.

CD5⁺DLBCL is known to have clinicopathologically and genotypically different characteristics from CD5⁻DLBCL (6-8). Patients with CD5⁺DLBCL show a high age at onset, a female predominance, frequent involvement of a variety of extranodal sites, and poor overall prognosis with a 5-year survival rate of 34% (6). High age, female sex, and involvement of an extranodal site in our patient all match the clinical features of CD5⁺DLBCL. In our case, the occurrence of DLBCL in the temporal bone, which is an extremely unusual site, may have depended on the peculiarity of CD5⁺DLBCL. Though our patient achieved complete remission, she will need careful follow-up hereafter.

We report a rare case of primary temporal bone lymphoma. Our case and a review of the literature show that malignant lymphoma should be taken into consideration as a differential diagnosis in cases of therapy-resistant ear disease.

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