

Original Article

Histopathological Characteristics of Lymphomas in the Upper Aerodigestive Tract: A Single-Institute Study in Japan

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We analyzed the histopathological characteristics of lymphomas biopsied from the upper aerodigestive tract between 2000 and 2014 at the National Cancer Center Hospital in Japan. Of a total of 309 consecutive cases, the following incidences were observed: mature B-cell neoplasms, 77% (n = 239); mature T- and NK-cell neoplasms, 20% (n = 63); classical Hodgkin lymphomas, 0.7% (n = 2); and lymphoblastic lymphomas, 2% (n = 5). Lymphomas were most frequently (57%) detected in the oropharynx. The majority of cases (89%) were mature B-cell neoplasms (diffuse large B-cell lymphoma, 60%; follicular lymphoma, 10%), and 10% of cases were mature T-cell neoplasms. Six cases of plasma cell neoplasm (4 primary and 2 secondary involvement) and 2 cases of plasmablastic lymphoma in the upper aerodigestive tract were observed. Two out of 3 cases of extraosseous plasmacytoma with available biopsy material were positive for EBER1. All 3 patients received irradiation and achieved complete response; 1 had not relapsed after 17 months and the remaining 2 relapsed as plasma cell myeloma and solitary plasmacytoma of the bone. Of 47 extranodal NK/T-cell lymphoma, nasal-type cases in the upper aerodigestive tract, 38 (81%) were present in the sinonasal region and the remaining 9 (19%) were in the oropharynx (n = 4), nasopharynx (n = 3), and oral cavity (n = 2). In conclusion, since both primary lymphoma and secondary involvement of lymphoma are often diagnosed using biopsied materials from the upper aerodigestive tract, pathologists and hematologists should recognize the characteristics of lymphoma in this tissue. [*J Clin Exp Hematop* 55(1) : 7-11, 2015]

Keywords: lymphoma, upper aerodigestive tract, plasma cell neoplasm, Epstein-Barr virus

INTRODUCTION

The upper aerodigestive tract includes the sinonasal region (nasal cavity and paranasal sinuses), Waldeyer's ring [nasopharynx, oropharynx (tonsil and root of tongue), and hypopharynx], and the oral cavity. The sinonasal region and the oral cavity are defined as extranodal sites. Waldeyer's ring is defined as a nodal site in the Ann Arbor staging system; however, it has pathological characteristics of both lymphoid (nodal) and mucosal (extranodal) tissues.

Biopsy of the upper aerodigestive tract is technically easier and less invasive than an open biopsy of the lymph node. Primary lymphomas as well as secondary involvement of

many types of malignant lymphoma are diagnosed by biopsies of the upper aerodigestive tract.

Various histopathological types of lymphoma may occur in the upper aerodigestive tract. In the sinonasal region, most lymphomas diagnosed in Western countries are diffuse large B-cell lymphomas (DLBCLs), while those in Eastern countries and South America are extranodal NK/T-cell lymphoma, nasal type (ENKTN).¹⁻⁵ DLBCLs are most commonly located in the paranasal sinuses, whereas ENKTNs are located in the nasal cavity.¹⁻³ In Waldeyer's ring, DLBCL is the most common type of lymphoma (70-80%),⁶⁻⁸ followed by mucosa-associated lymphoid tissue (MALT) lymphoma (15%), peripheral T-cell lymphoma (8%), follicular lymphoma (FL) (6%), and mantle cell lymphoma (3%).⁶

Plasmablastic lymphoma is an AIDS-associated high-grade B-lineage neoplasm with plasmacytic differentiation. It typically presents in the oral cavity and is positive for the Epstein-Barr virus (EBV).⁹ In contrast, approximately 80% of extraosseous plasmacytoma occurs in the head and neck region.¹⁰ The sinonasal region, tonsil, and nasopharynx are the most common primary sites for extraosseous

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plasmacytomas,¹¹ and they are usually negative for EBV.^{10,11}

The aim of this study was to delineate the histopathological characteristics of lymphoma in the upper aerodigestive tract, a common biopsy site, in the National Cancer Center Hospital in Japan.

MATERIALS AND METHODS

Patient selection

This study included 309 consecutive patients with lymphoma of the upper aerodigestive tract who were biopsied at the National Cancer Center Hospital in Tokyo, Japan, between 2000 and 2014. The biopsies were divided into 5 categories by location: sinonasal region, nasopharynx, oropharynx, hypopharynx, and oral cavity. Lymphomas of both primary and secondary involvement in the upper aerodigestive tract were included in this study. The biopsied sites and histopathological diagnoses were listed, and their histopathological features were analyzed. Moreover, plasma cell neoplasms or plasmablastic lymphomas were selected and analyzed for their EBV status and clinicopathological characteristics. Clinical information was obtained from the patients' medical records. Informed consent was obtained from all of the patients. The study was approved by the Institutional Review Board of the National Cancer Center.

Histopathological diagnosis

The biopsied materials were fixed in 10% neutral-buffered formalin, embedded in paraffin, cut into 4- μ m-thick sections, and stained with hematoxylin and eosin for routine histopathological evaluation. All specimens were diagnosed by 2 pathologists (AMM and HT) according to the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues published in 2008.¹² Immunohistochemical analysis of formalin-fixed, paraffin-embedded tissues was performed by standard procedures. Antibodies against the following antigens were used: CD3 (PS1, 1:25; Novocastra, Newcastle, UK), CD5 (4C7, 1:100; Novocastra), CD10 (56C6, 1:100; Novocastra), CD15 (MMA, 1:100; Becton Dickinson, Tokyo, Japan), CD20 (L26, 1:200; Dako, Glostrup, Denmark), CD23 (1B12, 1:100; Novocastra), CD30 (Ber-H2, 1:100; Dako), CD56 (1B6, 1:100; Novocastra), CD138 (MI15, ready for use; Leica, Newcastle, UK), ALK (ALK1, 1:200; Dako), Bcl-2 (124, 1:100; Dako), cyclin D1 (SP4, ready for use; Nichirei, Tokyo, Japan), granzyme B (GrB-7, 1:200; Dako), TIA-1 (26gA10F5, 1:1,000; Immunotech, Marseille, France), TdT (poly, 1:20; Dako), κ (poly, 1:20,000; Dako), and λ (poly, 1:40,000; Dako). *In situ* hybridization with an EBV-encoded small nuclear early region (EBER)-1 probe (Dako) was performed to detect possible EBV infection.

RESULTS

Distribution of lymphomas in the upper aerodigestive tract

The distribution of all 309 lymphoma cases that were biopsied from the upper aerodigestive tract and diagnosed is summarized in Table 1. Among this total of 309 cases, the following incidences were observed: mature B-cell neoplasms, 77% (n = 239); mature T- and NK-cell neoplasms, 20% (n = 63); classical Hodgkin lymphomas, 0.7% (n = 2); and lymphoblastic lymphomas, 2% (n = 5). Twenty-two percent (n = 69), 13% (n = 41), 57% (n = 176), 2% (n = 5), and 6% (n = 18) of the cases were biopsied from the sinonasal region, nasopharynx, oropharynx, hypopharynx, and oral cavity, respectively.

Lymphomas in the oropharynx

Lymphomas were most frequently (57%) detected in the oropharynx, the central area of Waldeyer's ring (Table 1). The majority (89%) of the cases were mature B-cell neoplasms, as follows: DLBCL, 60%; FL, 10%; DLBCL and FL, 6%; mantle cell lymphoma, 7%; and MALT lymphoma, 4%. Ten percent of the cases were mature T-cell neoplasms. Only 1 case of classical Hodgkin lymphoma was observed.

Clinicopathological characteristics of plasmacytoid neoplasms

Six cases of plasma cell neoplasm and 2 cases of plasmablastic lymphoma in the upper aerodigestive tract were found (Table 2). Of the 6 cases of plasma cell neoplasm, 4 were primary extraosseous cases [3 in the nasal cavity (Fig. 1), 1 in the oropharynx]. Two cases of extraosseous plasmacytoma in the nasal cavity were EBER1-positive, 1 in the oropharynx was EBER1-negative, and the EBER1 status of 1 was not available. All 3 patients with available clinical data received irradiation and achieved complete response. One patient had not relapsed after 17 months, whereas the remaining 2 relapsed: one as plasma cell myeloma and the other as solitary plasmacytoma of the bone. Two other cases, involvement of plasma cell myeloma, one in the hypopharynx and the other in the nasal cavity. The EBER1 status of one was negative, whereas that of the other was not available.

One case of plasmablastic lymphoma was present in the oropharynx, and another in the gingiva. One out of these 2 cases was EBER1-positive, although they were both HIV antigen/antibody-negative. They both received chemotherapy and achieved complete response.

Table 1. Histopathology of 309 cases of lymphoma biopsied from the upper aerodigestive tract

Histopathology	Total n = 309	Sinonasal region n = 69 (22%)	Nasopharynx n = 41 (13%)	Oropharynx n = 176 (57%)	Hypopharynx n = 5 (2%)	Oral cavity n = 18 (6%)
Mature B-cell neoplasms	239 (77%)	28 (41%)	35 (85%)	156 (89%)	5	16 (89%)
DLBCL	160 (52%)	19 (28%)	23 (56%)	105 (60%)	4	9 (50%)
FL	26 (8%)		6 (15%)	17 (10%)		3
DLBCL and FL	11 (3%)		1	10 (6%)		
Mantle cell lymphoma	16 (5%)		3	12 (7%)		1
MALT lymphoma	14 (5%)	3	2	7 (4%)		2
Burkitt lymphoma	4	2		2		
Plasma cell neoplasms	6 (2%)	5			1	
Plasmablastic lymphoma	2			1		1
CLL/SLL	2			2		
Mature T- and NK-cell neoplasms	63 (20%)	40 (58%)	4	17 (10%)	0	2
ENKTN	47 (15%)	38 (55%)	3	4		2
Peripheral T-cell lymphoma, NOS	5			5		
AITL	2			2		
Adult T-cell leukemia/lymphoma	5	1	1	3		
ALCL, ALK positive	1			1		
ALCL, ALK negative	2	1		1		
Involvement of EATL	1			1		
Classical Hodgkin lymphoma	2 (0.7%)	0	1	1	0	0
Lymphoblastic lymphoma	5 (2%)	1	1	2	0	1
B	2	1				1
T	3		1	2		

Percentages (%) are stated only when there are more than 5 incidences.

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; ENKTN, extranodal NK/T-cell lymphoma, nasal type; FL, follicular lymphoma; MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified

Table 2. Clinicopathological characteristics of 8 patients with plasma cell neoplasm or plasmablastic lymphoma in the upper aerodigestive tract

Case	Age/Sex	Past history	Diagnosis	Site	EBER1	Bone marrow involvement	Treatment and response	Outcome (month after diagnosis)
1	60/M		Extrasosseous plasmacytoma	Nasal cavity	+	-	RT 46 Gy, CR	No relapse (17 mon)
2	64/M		Extrasosseous plasmacytoma	Nasal cavity	+	-	RT 50 Gy, CR	Relapsed as plasma cell myeloma (4 mon), DOD (24 mon)
3	76/M		Extrasosseous plasmacytoma	Oropharynx	-	-	RT 60 Gy, CR	Relapsed as solitary plasmacytoma of the femur (48 mon), AWD (180 mon)
4	83/M		Extrasosseous plasmacytoma	Nasal cavity	NA	-	NA	NA
5	67/M		Involvement of plasma cell myeloma	Hypopharynx	NA	-	COP-MP, PR	DOD (34 mon)
6	76/F	Solitary plasmacytoma of the rib 7 years ago, RT, CR	Involvement of plasma cell myeloma	Nasal cavity	-	-	COP-MP, SD	AWD (89 mon)
7	19/M		Plasmablastic lymphoma	Oropharynx	-	-	LMB96, ¹⁶ CR	No relapse (32 mon)
8	63/M		Plasmablastic lymphoma	Gingiva	+	-	CHOP + RT, CR	No relapse (14 mon)

AWD, alive with disease; AWOD, alive without disease; COP-MP, cyclophosphamide, vincristine, and prednisone-melphalan and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; DOD, dead of disease; EBER1, Epstein-Barr virus-encoded small nuclear early region 1; NA, not available; PR, partial response; RT, radiotherapy; SD, stable disease

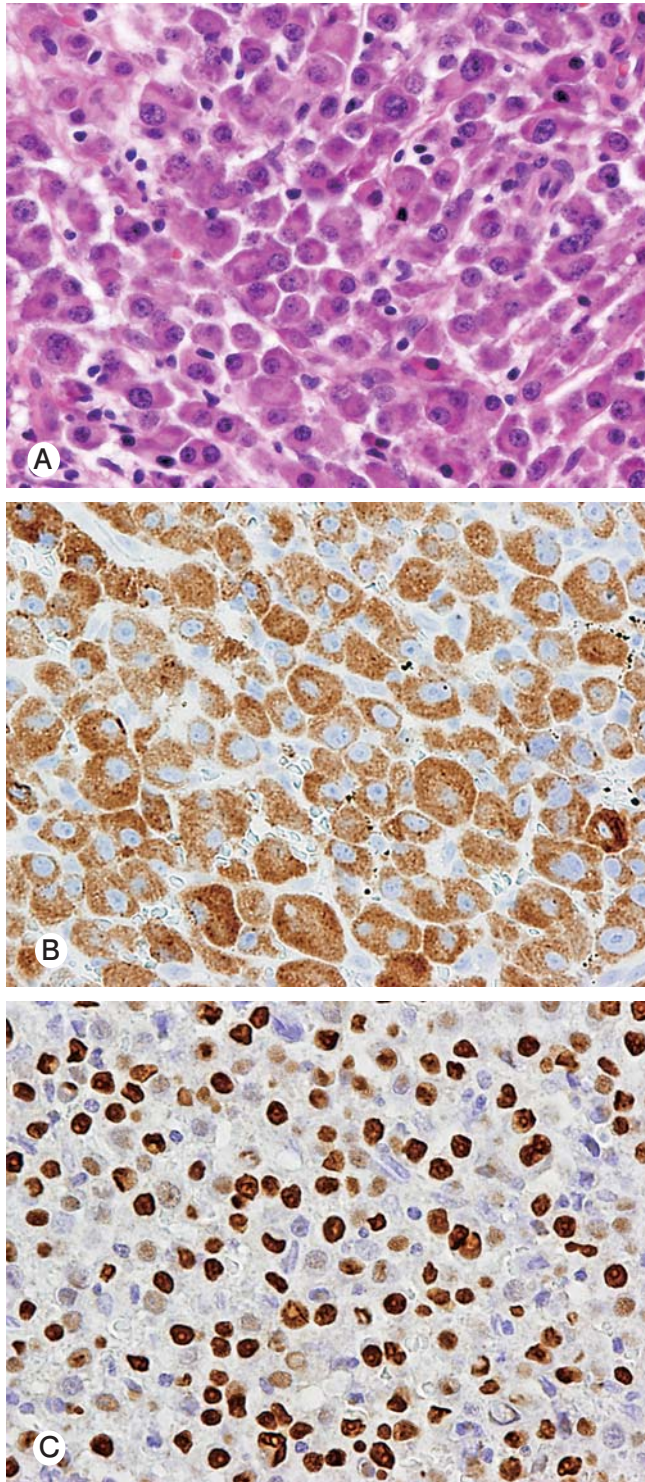


Fig. 1. A case of extraosseous plasmacytoma of the nasal cavity (Case 1) (*1A*, H & E stain, $\times 400$). Diffuse proliferation of medium-sized atypical plasmacytoid cells is seen. The tumor cells are positive for CD138 (*1B*, $\times 400$) and EBER1 (*1C*, $\times 400$).

Distribution of ENKTN

Of a total of 65 patients with lymphomas of the sinonasal region, ENKTN (55%) was the most frequently observed, followed by DLBCL (28%), extraosseous plasmacytoma (7%), and MALT lymphoma (4%). However, not all NK/T-cell lymphomas in the sinonasal region were ENKTN, as 1 case of adult T-cell leukemia/lymphoma and 1 of anaplastic large cell lymphoma (ALK-negative) were seen. These 2 cases were negative for EBER1. Of a total of 47 ENKTN cases in the upper aerodigestive tract, 38 (81%) were seen in the sinonasal region, while the remaining 9 (19%) were detected in the oropharynx ($n = 4$), nasopharynx ($n = 3$), and oral cavity ($n = 2$). Of the latter 9 cases, all were positive for EBER1 and cytotoxic molecules (TIA-1 and/or granzyme B), and 7 out of 9 cases (78%) were positive for CD56.

DISCUSSION

Among all of the nodal and extranodal lymphomas examined in the Kantou area of Japan, where the National Cancer Center Hospital is located, the incidence of mature B-cell lymphoma was reported to be 69%, including DLBCL (35%), FL (19%), and other types (15%). The incidence of mature T/NK-cell lymphoma was 20%, and that of Hodgkin lymphoma was 9%.¹³ In the present study for lymphomas in the upper aerodigestive tract, the incidences of histological subtypes were similar to those previously reported in the Kantou area; however, the incidence of DLBCL (52%) was higher, whereas that of classical Hodgkin lymphoma (0.7%) was lower.

The oropharynx is the central area of Waldeyer's ring, and is the part of the aerodigestive tract where over half (57%) of lymphomas were diagnosed in the present study. Waldeyer's ring was defined as a nodal region in the Ann Arbor staging system. The distribution of histopathological subtypes of lymphoma in the oropharynx was similar to previously reported statistics in the Kantou area.¹³ However, some differences were observed: the incidence of MALT lymphoma was 4% ($n = 7$), which was higher than that of MALT lymphoma in the Kantou area (1.5-1.8%).¹ This may be because Waldeyer's ring has both lymphoid (nodal) and mucosal (extranodal) characteristics. In addition, some ENKTNs and plasma cell neoplasms/plasmablastic lymphomas were observed in the oropharynx. These neoplasms were seen throughout the upper aerodigestive tract.

Extraosseous plasmacytoma often occurs in the upper aerodigestive tract and is reported to be EBER1-negative.^{10,11} In the present study, 4 out of 6 cases were primary tumors and the other 2 cases, involvement of plasma cell myelomas. The upper aerodigestive tract may thus not only be a common site for extraosseous plasmacytoma, but also for the involvement of plasma cell myeloma. EBER1

was positive in 2 out of 3 available primary cases. In Asian countries, therefore, primary extranodal plasmacytoma in the upper aerodigestive tract might also be associated with EBV; the virus may not be solely associated with plasmablastic lymphoma.

The majority of ENKTNs were observed in the sinonasal region; however, 19% (n = 9) of ENKTN cases were observed in the upper aerodigestive tract other than the sinonasal region. In 2 previous reports,^{14,15} patients with nasal ENKTN, including ENKTN of the upper aerodigestive tract other than the nasal cavity, showed more favorable prognosis than patients with non-nasal ENKTN. Hence, better detection of ENKTN in the upper aerodigestive tract other than in the sinonasal region is important, and patients should be treated similarly to patients with ENKTN in the sinonasal region if diagnosed.

In conclusion, since both primary lymphoma and secondary involvement of lymphoma are often diagnosed using biopsied materials from the upper aerodigestive tract, both pathologists and hematologists should obtain a better understanding of the characteristics of lymphoma in the upper aerodigestive tract.

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DISCLOSURE STATEMENT

CONFLICTS OF INTEREST: There are no conflicts of interest to declare.

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