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Case report

A Case of Composite Lymphoma with Extranodal NK/T-cell Lymphoma, Nasal-type and Diffuse Large B-cell Lymphoma

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Composite lymphoma (CL) is defined as the occurrence of two distinct types of lymphoma within the same patient. Most cases of CL involve Hodgkin and non-Hodgkin lymphomas or two distinct types of B-cell lymphomas; true CL is a composite B-cell and T-cell lymphoma, and is rare. We herein report a case involving concurrent extranodal NK/T-cell lymphoma, nasal-type and diffuse large B-cell lymphoma, which has not been previously reported. As the mechanisms and treatments of composite B-cell and T-cell lymphomas are unclear, further studies are required to improve the prognosis.

Keywords: Composite lymphoma; Extranodal NK/T-cell lymphoma, nasal-type; Therapy management; Epstein-Barr virus

INTRODUCTION

Composite lymphoma (CL) is defined as the occurrence of two distinct types of lymphoma within the same patient. In CL, the lymphomas typically occur concurrently, usually together within the same organ; however, cases in which two distinct lymphomas presenting sequentially are also classified as CL.[1] CL has been reported to account for 1-4% of lymphomas.[2]

Histologically, CL is composed of a Hodgkin lymphoma (HL) component and a non-Hodgkin lymphoma (NHL) component, or two distinct NHL components.[1] However, most cases are caused by clonal transformation resulting in two distinct B-cell lymphoma components or are composed of HL and NHL components that originate from a common germinal center B-cell precursor.[3] Thus, composite B-cell and T-cell lymphomas are considered to be true CL.[4,5]

There are a few reports of composite B-cell and T-cell lymphomas.[6-9] These rare cases include several B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic lymphoma (CLL), combined with T-cell lymphomas, including angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) and anaplastic large cell lymphoma (ALCL). Very few CL cases with natural killer (NK) cell lymphoma have been reported.[10-12]

To assess the frequency of CL at our institution, we reviewed the pathological records of patients treated between 2007 and 2016, and identified 2 CL cases among 1742 (0.11%) cases of malignant lymphoma. We herein report one case: rare CL composed of extranodal NK/T-cell lymphoma, nasal-type (ENKL), and DLBCL.

CASE PRESENTATION

A 61-year-old woman (case 1 in Table 1 and 2) complained of nasal congestion, nasal discharge and atypical genital bleeding. Laboratory testing revealed the following findings: hemoglobin, 8.5 g/dL; platelet count, 25.4×10^9/L;

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Table 1. Clinical data of true composite lymphomas including an aggressive NK-cell tumor from our institution (Case 1) and from the literature (Cases 2 and 3).

Case No.	Age (y) at first diagnosis / Sex	Immuno deficiency	First diagnosis	Second diagnosis	Time from 1st to 2nd diagnosis (months)	Pathological type	Detection of tumor cells	Clinical Stage (Cs)	Elevated LD (U/L)	sIL-2R (U/mL)	Treatment	Clinical Course	Outcome / follow-up (months)	References
1	61 / F	-	ENKL	DLBCL	concurrently	ENKL	Nasal Cavity	IIIA	550	2920	R-CHOP×6→CR, CHASER×2, VP-16 →CR2	2nd CR	Alive / 49	current case
						DLBCL	Uterine cervix							
2	52 / F	mosquito-bite hyper-sensitivity	Cytotoxic T-cell lymphoma	ANKL	concurrently	Cytotoxic T-cell lymphoma	Inguinal LN	IIIB	861	4700	Steroid	Non CR	Dead / 8 days	[12]
						ANKL	BM	NS						
3	29 / M	-	MC-CHL	ANKL	19Y	MC-CHL	Subclavicular LN	IIIB	NS	NS	CHOP like×6	CR	Dead / 1	[13]
						ANKL	BM	NS	NS	14026	VP-16	Non CR		

ANKL, aggressive NK-cell leukemia; DLBCL, diffuse large B-cell lymphoma; ENKL, extranodal NK / T-cell lymphoma, nasal type; MC-CHL, mixed cellularity classical Hodgkin lymphoma
BM, bone marrow; CR, complete remission; LD, Lactate dehydrogenase level; sIL-2R, soluble interleukin-2 receptor

Table 2. Pathological data of true composite lymphomas including an aggressive NK-cell tumor from our institution (Case 1) and from the literature (Cases 2 and 3).

Case No.	Pathological type	Immunohistochemistry														
		CD3	CD4	CD5	CD7	CD8	CD10	CD15	CD16	CD20	CD30	CD56	BCL-2	BCL-6	MUM-1	EBER
1	ENKL	+	-	-	NS	NS	-	NS	NS	-	NS	-	NS	NS	NS	+
	DLBCL	-	-	-	-	-	+	NS	NS	+	NS	-	+	+	-	-
2	Cytotoxic T-cell lymphoma	+	-	-	NS	+	NS	NS	NS	-	NS	-	NS	NS	NS	+
	ANKL	-	-		NS	-	NS	NS	+	NS	NS	+	NS	NS	NS	+
3	MC-CHL	-	-	NS	-	-	NS	+	NS	-	+	-	NS	NS	NS	+
	ANKL	+	-	NS	-	-	+	-	NS	-	-	+	NS	NS	NS	+

ANKL, aggressive NK-cell leukemia; DLBCL, diffuse large B-cell lymphoma; ENKL, extranodal NK / T-cell lymphoma, nasal type; MC-CHL, mixed cellularity classical Hodgkin lymphoma
EBER, EB virus-encoded small RNAs; NS, not specified

leukocyte count, 5.7×10^9/L without atypical cells; lymphocyte count, 0.60×10^9/L; lactase dehydrogenase, 550 U/L (high); soluble interleukin-2 receptor, 2,920 U/mL (high); immunoglobulin G (IgG), 371 mg/dl; immunoglobulin A (IgA), 51 mg/dl; immunoglobulin M (IgM), 48 mg/dl. The patient was negative for hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and human T-cell leukemia virus type 1 (HTLV-1). Her Epstein-Barr virus (EBV) status was positive for EBV viral capsid antigen (VCA)-IgG, but negative for EBV VCA-IgM and EBV nuclear antigen (EBNA), suggesting that she was in the recovery phase from either initial or chronic EBV infection.

Nasal cavity biopsy demonstrated the infiltration of medium-sized lymphoma cells with constricted nuclei; the cells were CD 3 (+), CD 4 (-), CD 5 (-), CD 56 (-), TIA-1 (+) and EBV-encoded RNA (EBER) *in situ* hybridization (ISH) (+) (Figure 1).

In order to observe the spread of the lesions, positron emission tomography-computed tomography (PET-CT) was performed after the biopsy, and the accumulation of 18F-fluorodeoxy glucose (FDG) was observed in the mediastinal nodes, pleura, mesenteric nodes, uterus (bulky mass) and pelvic nodes (Figure 2). Bone marrow invasion was not noted by bone marrow biopsy.

Uterine cervix biopsy demonstrated the diffuse infiltration of medium to large-sized aberrant lymphoma cells. These cells were CD 10 (+), CD 20 (+), bcl-2 (+), bcl-6 (+), MUM-1 (-), EBER-ISH (-) and MIB-1 (+) (MIB-1 index; 90%) (Figure 3). Lymphoma-like lesions in the cervix, which were benign lymphoid hyperplasia simulating

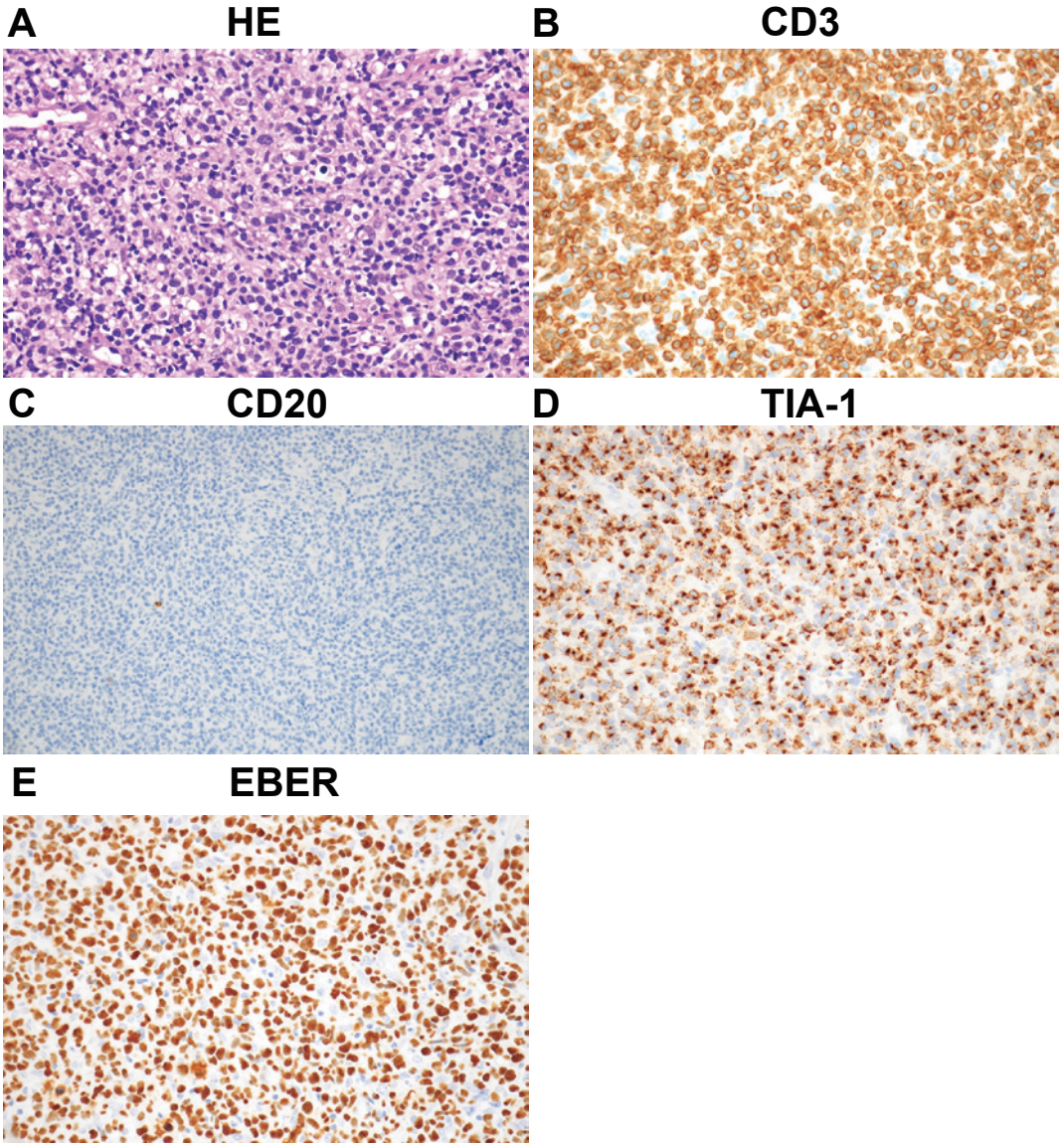

Fig. 1. The histological appearance of ENKL in case 1.
(***A***) The infiltration of lymphoma cells in the nasal cavity (HE 400×).
(***B***), (***C***), (***D***), (***E***) The immunohistochemical analysis of CD 3 (400×), CD 20 (400×), TIA-1 (400×) and EBER (400×). The immunohistochemical analysis demonstrated positivity for CD 3, TIA-1 and EBER, and negativity for CD 20.

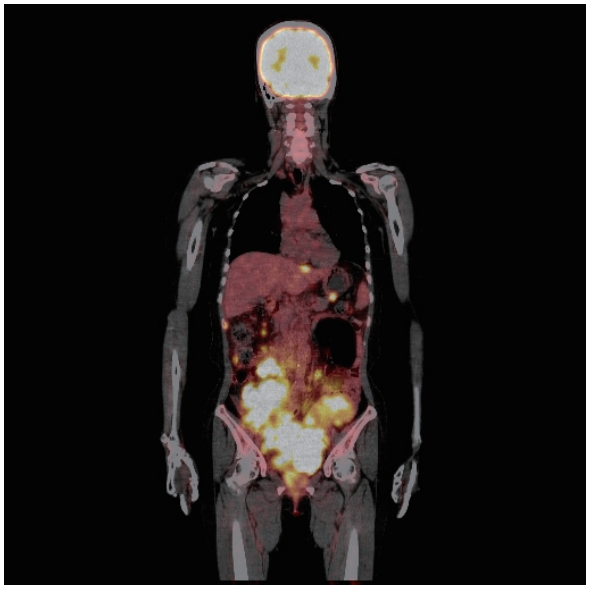

Fig. 2. PET-CT before treatment.
PET-CT was performed after the biopsy of the nasal tumor. Accumulation of FDG was noted in the mesenteric nodes, mediastinal nodes, pleura and pelvic mass.

malignant lymphoma, were excluded, as this patient had a bulky uterine mass.[13]

The patient was finally diagnosed with composite lymphoma composed of ENKL in the nasal cavity and uterine DLBCL. Chromosomal analyses of the nasal cavity biopsy or uterine cervix biopsy were not performed.

Complete remission (CR) was achieved with 8 cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone). DLBCL but not ENKL relapsed at 7 months after achieving CR. Combination chemotherapy with 2 cycles of CHASER (rituximab, cyclophosphamide, cytarabine, etoposide and dexamethasone) and 1 cycle of etoposide were administered, resulting in 2nd CR. Autologous hematopoietic stem cells were unable to be harvested from her peripheral blood because of poor mobilization after etoposide treatment. She remained alive for 49 months from the diagnosis without a 2nd recurrence of either type of lymphoma.

DISCUSSION

The present case involved rare CL with concurrently-developed ENKL, and DLBCL that exhibited typical pathological and immunohistochemical patterns for each lymphoma subtype as they were diagnosed. In addition, the clinical features and consequences of the case were in line with the predictions. No CL cases with the simultaneous occurrence of ENKL have been previously reported. This is the first report of CL with the concurrent development of ENKL and DLBCL.

Regarding aggressive NK-cell malignancies, only 2 cases of CL with aggressive NK-cell leukemia (ANKL) have previously been reported (cases 2 and 3 in Table 1 and 2), a spectrum of ENKL that is strongly associated with EBV infection.[10,11] The cases included one concurrent case of ANKL and cytotoxic T-cell lymphoma (case 2),[12] and one sequential case, in which ANKL was diagnosed after treatment for HL (case 3).[14] These complicating lymphomas, including HL and cytotoxic T-cell lymphoma, are also known as EBV-related disease.[15] Indeed, EBV was detected in the complicating lymphomas as well as in ANKL. Regarding the patient background, the patient in case 2 had a history of mosquito-bite hypersensitivity since childhood, which is known to be closely related to chronic EBV infection and NK cell leukemia/lymphoma.[12] The patient in case 3 underwent chemotherapy to treat HL at 29 years of age.[14] Continuous EBV infection may have led to the development of ANKL and combined lymphoma in these cases. In case 1, EBER was only detected in the ENKL lesion and not in the concurrent DLBCL lesion. The lymphomagenesis of DLBCL in case 1 may differ from that in the reported CL cases with aggressive NK malignancy.

There have been several hypotheses about the pathogenesis of CL. CL may develop in cases involving prolonged immunosuppression such as rheumatoid arthritis or celiac disease.[16] Age-related decline in immune function may also be responsible for the pathogenesis of CL. Suefuji *et al*. reported that 24 of 29 patients with composite B-cell and T-cell lymphomas were over 60 years of age.[6] Case 1 developed in a patient over 60 years of age at the time of diagnosis with no apparent history of illness related to immunosuppression or recurrent infectious episodes. However, her immunoglobulin level was markedly low. Thus, the two lymphomas in case 1 were presumed to have arisen coincidentally through immunosuppression due to an unknown cause in addition to an age-related decline in immune function.

The disease components need to be considered when deciding the therapeutic strategy for CL. When CL occurs sequentially, the treatment strategy is simple. Treatment for emerging lymphoma is preferred because the course is similar to that when a single lymphoma occurs alone.[17] When CL occurs concurrently with aggressive B-cell lymphoma, patients are frequently treated with the R-CHOP regimen.[18] Concurrent B-cell and T-cell lymphoma is treated with an anti-CD 20 antibody-containing protocol, and the treatment outcome is dependent on the T-cell lymphoma.[4,6,19] In the case of CL with ANKL or ENKL, concurrent chemoradiotherapy consisting of radiotherapy and a two-thirds dose of DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin) is preferable to R-CHOP, and it should be administered before R-CHOP according to the treatment strategy for localized ENKL.[20] However, case 1 was initially treated using R-CHOP because the case involved numerous lesions with a bulky DLBCL mass. The DLBCL but not ENKL relapsed and the patient was rescued by salvage chemotherapy. As DLBCL relapsed despite the antecedent R-CHOP therapy, the initial treatment with R-CHOP was considered appropriate.

In conclusion, we reported the first case of CL involving the combination of ENKL and another B-cell lymphoma. Composite B-cell and T-cell lymphoma is rare, and the disease mechanisms and optimal treatment strategies remain

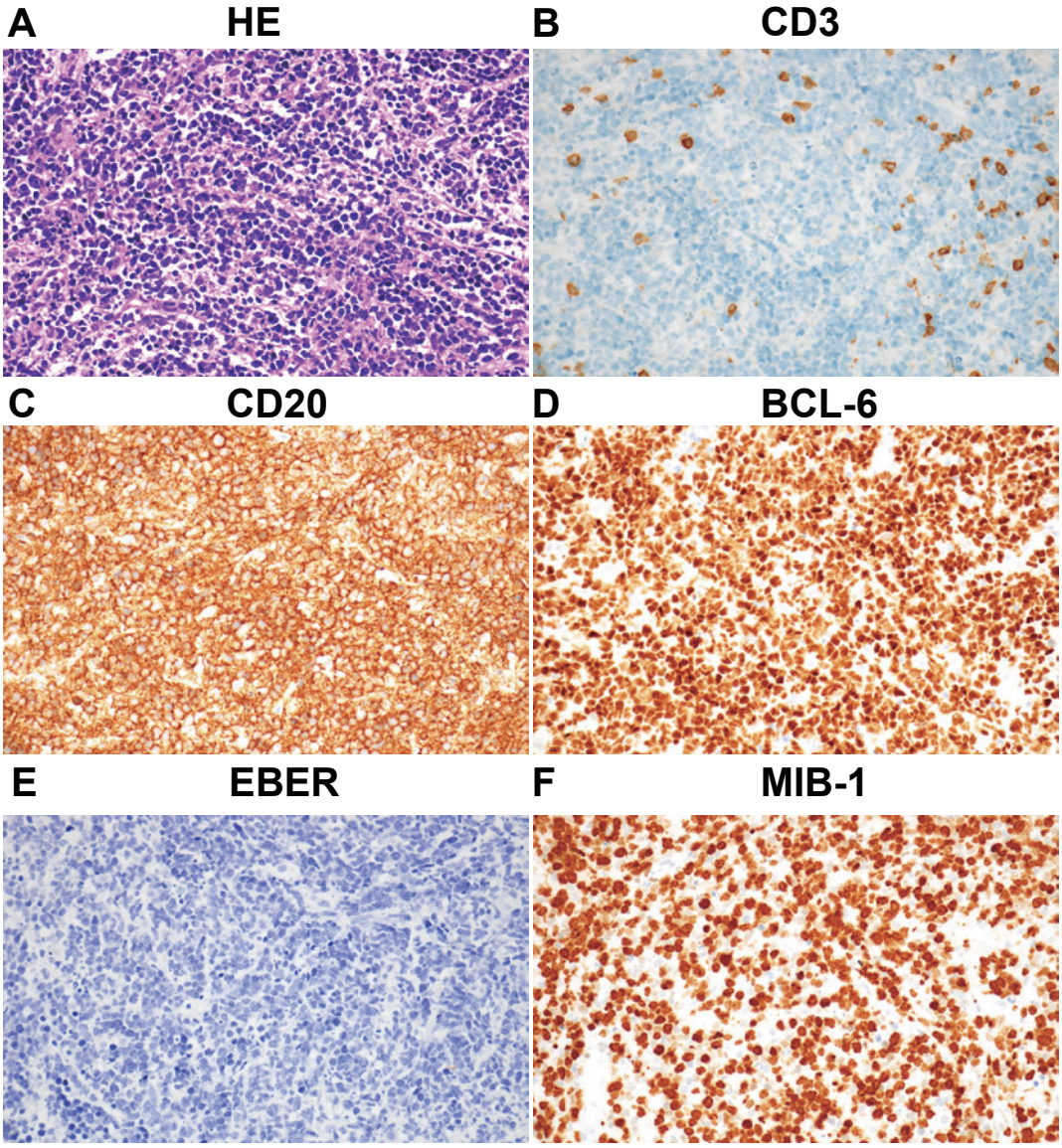

Fig. 3. The histological appearance of DLBCL in case 1.
(***A***) Infiltration of lymphoma cells in the uterine cervix (HE 400×).
(***B***), (***C***), (***D***), (***E***), (***F***) The immunohistochemical analysis of CD 3 (400×), CD 20 (400×), BCL-6 (400×), EBER (400×) and MIB-1 (400×). The immunohistochemical analysis demonstrated positivity for CD 20, BCL-6 and MIB-1, and negativity for CD 3 and EBER.

uncertain. Further analyses with more cases will be necessary to improve the prognosis.

AUTHOR CONTRIBUTIONS

H.K., collection and assembly of data, data analysis and interpretation, and manuscript writing; H.M., conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing; S.K., D.F., S.S-H., A.I., H.R., Y.A., R.S., S.M., M.O., Y.S., Y.O. and H.K, collection and assembly of the data; N.N., data analysis and interpretation, and manuscript writing; K.A., conception and design, administrative support, data analysis and interpretation, manuscript writing and final approval of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

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