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A Clinicopathological Study of 20 Patients With T/Natural Killer (NK)-Cell Lymphoma–Associated Hemophagocytic Syndrome With Special Reference to Nasal and Nasal-Type NK/T-Cell Lymphoma

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Abstract

We describe the clinicopathological features of 20 patients with T/natural killer (NK)-cell lymphoma–associated hemophagocytic syndrome (T/NK-LAHS). These patients were categorized into 2 groups according to the onset of hemophagocytic syndrome (HPS). Group 1 developed HPS during the clinical course, typically at the terminal phase of the disease. This group consisted of 7 patients with extranodal lymphoma arising in the nasal cavity, paranasal cavity, tonsils, or skin at presentation. In 5 of these patients, the preferred diagnosis was nasal and nasal-type NK/T-cell lymphoma, whereas the disease diagnoses in the remaining 2 patients were peripheral T-cell lymphoma of unspecified type and angioimmunoblastic T-cell lymphoma, respectively. Group 2 consisted of 13 patients whose disease corresponded to so-called malignant histiocytosis-like lymphoma, which is characterized by HPS at the initial presentation and the infiltration of the liver, spleen, and/or bone marrow without tumor formation. Nine of these 13 cases were found to have common histopathological features: $CD56^+$, Epstein-Barr virus positivity, cytotoxic molecules, and nasal-type NK/T-cell lymphoma. The very poor prognosis of T/NK-LAHS may be partly explained by the finding that nasal and nasal-type NK/T-cell lymphoma, which is resistant to standard chemotherapy, made up the highest percentage (70%) of the cases. *Int J Hematol.* 2001;74:303-308.

Key words: Lymphoma-associated hemophagocytic syndrome; Nasal and nasal-type NK/T-cell lymphoma; Epstein-Barr virus; CD56; Cytotoxic molecules

1. Introduction

T/natural killer (NK)-cell lymphoma associated with hemophagocytic syndrome (HPS) has been mainly reported in Asia, most notably in Japan, Hong Kong, and Taiwan [1-7]. In 1994, Chubachi and Miura proposed the terminology of lymphoma-associated hemophagocytic syndrome (LAHS) for the malignant histiocytosis (MH)-like phenomenon arising in patients with malignant lymphoma [8]. We retrospectively reviewed 69 cases of adult LAHS and concluded that the cases could be clinicopathologically categorized into 2 groups according to the time of onset of HPS, the primary sites, and the pathological characteristics of the lymphomas. Group 1 (32 cases) was characterized by 2 common features: first, the histology of angiocentric and/or angiodestructive lesions, which was originally described by Jaffe et al [9], and second, the relatively late onset of HPS at relapse or during the progressive state of lymphoma. Group 2 (35 cases) featured the clinical diagnosis of MH, which was defined by Falini et al [10]. In contrast to group 1, however, HPS in group 2 developed at the initial manifestation with variable pathological diagnoses.

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In 1994, Yao et al analyzed 12 patients with Epstein-Barr virus (EBV)-positive T/NK-LAHS and subdivided them into 2 groups based on their disease characteristics: angioinvasive-type peripheral T-cell lymphoma (PTCL) and MH-like PTCL [11], which clinically correspond to groups 1 and 2, respectively, in the present study. However, little has been known about the clinicopathological relationship between the 2 groups.

The relationship between groups 1 and 2 may be interpreted in 2 ways. One is that these 2 groups are simply different clinicopathological entities. The other is that the 2 groups are in fact the same disease but at different stages of development. This latter view results from shared pathological features in the 2 groups. Group 1 comprises cases presenting as extranodal lymphomas that developed into infiltration of the bone marrow, liver, and spleen. However, as in the second interpretation above, group 2 appears to include only those cases at the advanced stages of the same disease. In this instance, lesions of the nose, paranasal cavity, and skin may be evident under close examination.

In this study, we examined the clinicopathological features of 20 cases of T-cell or NK-cell lymphoma-associated hemophagocytic syndrome (T/NK-LAHS).

2. Materials and Methods

2.1. Diagnostic Criteria and Patients

Twenty patients with T/NK-LAHS treated at Akita University Hospital or its affiliated hospitals were included in this study. Their clinical findings were collected between January 1990 and December 1999. We adopted the following criteria to make a diagnosis of T/NK-LAHS: (1) hematologically readily identifiable hemophagocytic histiocytes in the bone marrow and (2) pathologically and immunophenotypically proven malignant lymphoma of T/NK-cell type that was indicated by the expression of CD2, cCD3, or CD45RO and no expression of B-cell markers. All the cases were reviewed histologically and immunophenotypically, and they were subsequently assigned according to the scheme of the World Health Organization (WHO) classification [12].

All the cases of T/NK-LAHS were categorized into 2 groups based on the time of onset of HPS, as originally defined by Chubachi and Miura [8]. Group 1 patients (n = 7) developed HPS during the clinical course, typically at the advanced stage of lymphoma. In contrast, group 2 patients (n = 13) presented with HPS at the diagnosis of lymphoma.

2.2. Immunophenotypic Analysis

The materials were fixed in buffered formalin, embedded in paraffin wax, and stained with hematoxylin-eosin. Immunostaining was performed using an avidin-biotin peroxidase complex method. The panel of monoclonal antibodies used for this study was as follows: CD3, CD8, CD45RO, CD20, (Bioscience Products, Emmenbruke, Switzerland), CD2, CD4, CD5, CD56 (Novocastra Laboratories, Newcastle, UK), T-cell–restricted intracellular antigen (TIA)-1 (Coulter Immunology, Hialeah, FL, USA), and granzyme B (Monosan, Uden, the Netherlands).

2.3. In Situ Hybridization Analysis for EBV

Assessment for EBV was performed on formalin-fixed paraffin-embedded sections by in situ hybridization using EBER (EBV-encoded early RNAs) oligonucleotides [13]. In short, a DAKO hybridization kit (Dako Corp, Carpinteria, CA, USA) was used with a cocktail of fluorescein isothiocyanate (FITC)-labeled EBER oligonucleotides (DAKO A/S code Y017). Hybridization products were detected using a mouse monoclonal anti-FITC (DAKO M878) and a Vectastain ABC kit (Vector Laboratories, Burlingame, CA, USA).

3. Results

3.1. Clinical Findings

The clinical features at the diagnosis of lymphoma are summarized in Table 1. The median ages of patients in group 1 and group 2 were 58 and 43 years old, respectively. The ratio of men to women was not significantly different between the 2 groups. Extranodal diseases, including nasal cavity, paranasal cavity, and subcutaneous tumors, were noted in group 1. All the patients in group 2 had hepatosplenomegaly without nodal lesions at presentation, except for cases 8, 9, and 17. Paranasal cavity and subcutaneous tumors were noted in 3 of the cases during the clinical course. All the patients in group 1 exhibited stage I of the Ann Arbor staging system, except for the case 2 patient, who exhibited peripheral lymphadenopathy. However, group 2 patients were all at stage IV at the onset of lymphoma.

The clinical features at the onset of HPS are summarized in Table 2. High-grade fever and hepatosplenomegaly were common in both groups, although the patients' performance statuses were variable. There were no significant differences between the clinical features of the 2 groups at the onset of HPS.

Table 3 shows the laboratory findings at the onset of HPS. All of the patients showed anemia (hemoglobin, <9 g/dL) and/or thrombocytopenia (platelet count, <100,000/μL). Although all the patients showed leukocytopenia except case 8 and case 13, only four patients showed agranulocytosis. Leukemic stage was not observed in the present series. All cases except for case 1 showed increased levels of lactate dehydrogenase (LDH) and ferritin, although levels of triglyceride (TG) and fibrin degradation product (FDP) were variable. The percentages of histiocytes and lymphoma cells in bone marrow were variable, but bone marrow showed a hyponormocellular tendency in this series. There were also no significant differences between the 2 groups in the laboratory findings at the onset of HPS.

All patients received standard chemotherapy including doxorubicin, vincristine, cyclophosphamide, and prednisolone except for cases 8 and 18. Five cases in group 1 and all cases in group 2 showed a poor response to chemotherapy (Table 4). The survival curves of the 2 groups after the onset of HPS showed similar poor prognoses (median survival: 46 days in group 1 and 34 days in group 2, $P = .2511$ by the log rank test) (Figure 1).

Table 1.
Clinical Findings at the Diagnosis of Malignant Lymphoma*

Case No.	Age/Sex	Site of Biopsy	Other Sites Involved	Stage	Initial Diagnosis According to the WF With Minor Modification
Group 1					
1	65/F	Subcutaneous tumor	None	I	ML, large cell, immunoblastic
2	70/M	Tonsil, LN	None	III	AILD-like T-cell lymphoma
3	41/F	Nasal cavity	None	I	ML, diffuse mixed, small and large cell
4	22/F	Subcutaneous tumor	None	I	ML, diffuse large cell
5	58/M	Paranasal cavity	None	I	ML, large cell, immunoblastic
6	27/M	Subcutaneous tumor	None	I	ML, diffuse mixed, small and large cell
7	78/F	nasal cavity	None	I	ML, diffuse mixed, small and large cell
Group 2					
8	69/F	Liver, spleen, LN	BM, kidney	IV	ML, large cell immunoblastic
9	59/M	LN, BM	Liver, spleen	IV	ML, diffuse large cell
10	39/F	Liver, spleen	BM	IV	ML, diffuse mixed, small and large cell
11	68/M	Liver, spleen	BM, pulmonary	IV	ML, diffuse large cell
12	66/M	Liver	Spleen, BM	IV	ML, diffuse large cell
13	17/F	Spleen	Liver, BM	IV	ML, diffuse large cell
14	36/M	BM	Liver, spleen	IV	ML, NOS
15	16/M	BM	Liver, spleen	IV	ML, NOS
16	69/M	BM	Liver, spleen	IV	ML, NOS
17	43/F	LN	Liver, spleen, BM	IV	ML, large cell, immunoblastic
18	49/M	Paranasal cavity	Liver, spleen, BM	IV	ML, diffuse large cell
19	17/F	Subcutaneous tumor	Liver, spleen, BM	IV	ML, diffuse large cell
20	23/M	Subcutaneous tumor	Liver, spleen, BM	IV	ML, diffuse large cell

*WF indicates working formulation; ML, malignant lymphoma; LN, lymph node; AILD, angioimmunoblastic lymphadenopathy with dysproteinemia; BM, bone marrow; NOS, not otherwise specified.

3.2. Pathological Findings

An immunophenotypic analysis showed that the tumor cells had CD2, cCD3, or CD45RO, which indicate a T/NK-cell phenotype (Table 5). These tumor cells expressed CD56 in 3 of 7 patients in group 1 and in 8 of 13 patients in group 2. The EBV by EBER in situ hybridization showed positive signals in 5 of 7 patients in group 1 and in 9 of 13 patients in group 2. The cytotoxic granule-associated protein, TIA-1 or granzyme B (cytotoxic molecule [CM]), was detected by

Table 2.
Clinical findings at the Onset of Hemophagocytic Syndrome

Case No.	Fever	Superficial Lymphadenopathy	Hepatomegaly	Splenomegaly	Rash	Performance Status
Group 1						
1	+	+	+	+	+	3
2	+	+	+	+	–	4
3	+	+	+	–	–	3
4	+	–	+	+	+	2
5	+	–	+	+	–	3
6	+	–	+	+	+	1
7	+	–	+	–	–	3
Group 2						
8	+	–	+	+	–	4
9	+	+	+	+	+	3
10	+	–	+	+	+	4
11	+	–	+	+	+	1
12	+	–	+	+	+	3
13	+	+	+	+	–	3
14	+	–	+	+	–	3
15	+	+	+	+	–	2
16	+	–	–	+	–	4
17	+	+	+	+	–	3
18	+	–	–	+	–	3
19	+	+	+	–	–	1
20	+	–	+	+	+	1

Table 3.
Laboratory Findings at the Onset of Hemophagocytic Syndrome*

Case No.	WBC, /μL	ANC, /μL	Hb, g/dL	PLT, /μL	LDH×	TG, mg/dL	Ferritin, ng/dL	FDP, μg/mL	BM Cellularity	Histiocytes in BM, %	Lymphoma Cells in BM, %
Group 1											
1	3100	2542	8.9	5000	0.5	NA	NA	9.4	Hypocellular	1.1	0.6
2	900	486	12.2	17,000	7.9	100	8952	42.6	Hypocellular	14.0	5.0
3	2800	2128	8.2	15,000	2.5	253	2741	2.6	Hypocellular	2.2	44.4
4	1400	896	6.3	105,000	3.2	240	53,074	5.5	Normocellular	3.3	2.8
5	2300	1219	9.0	17,000	19.1	206	1990	13.8	Hypercellular	1.5	53.0
6	2830	1924	7.7	12,000	1.9	133	3860	4.8	Normocellular	12.0	+
7	2400	1776	10.3	57000	9.4	193	9276	11.2	Normocellular	2.4	10.2
Group 2											
8	64,100	40,063	10.8	34,000	34.5	156	NA	NA	Hypercellular	+	+
9	300	6	7.0	70,000	5.4	NA	3960	89.3	Hypocellular	10.8	20.0
10	1400	1022	7.5	60,000	3.4	NA	1156	NA	Hypocellular	11.0	43.0
11	1600	928	11.7	56,000	1.6	99	7605	0	Normocellular	17.0	4.0
12	2800	1677	12.6	101,000	1.6	181	8000	0	Normocellular	6.0	+
13	4200	3318	10.6	19,000	5.0	NA	NA	10.3	Hypocellular	24.8	+
14	2300	1495	7.4	13,000	4.9	208	2480	47.0	Normocellular	+	30.4
15	500	390	7.5	19,000	3.2	387	NA	14.6	Hypocellular	22.0	3.0
16	500	330	7.1	49,000	18.3	NA	75,910	80.1	Normocellular	8.0	12.7
17	1400	966	7.4	32,000	3.2	NA	NA	13.7	Normocellular	+	19.6
18	1300	1079	8.0	11,000	8.3	378	52,300	15.0	Normocellular	6.0	3.0
19	1800	1026	10.4	63,000	2.3	242	8737	15.2	Normocellular	4.0	1.2
20	2300	1196	12.0	82,000	7.0	159	5585	4.0	Normocellular	5.6	1.8

*WBC indicates white blood cell count; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet count; LDH×, lactate dehydrogenase upper limit; TG, triglyceride; FDP, fibrin degradation product; BM, bone marrow; NA, not available.

immunohistochemical studies in 5 of 7 patients in group 1 and in 12 of 12 patients in group 2.

Combined with these immunophenotypic and histopathological findings, 5 of 7 patients in group 1 and 9 of 13 patients in group 2 shared the following features: $CD56^+$, EBV^+, and CM^+. Furthermore, these patients developed the same nasal and nasal-type NK/T-cell lymphoma (Table 6). The other histopathological diagnoses included peripheral T-cell lymphoma of unspecified type in group 1, angioimmunoblastic T-cell lymphoma in group 1, 2 cases of EBV^- $CD8^+$ cytotoxic

Table 4.
Response to Therapy and Clinical Outcome

Case No.	Response	Survival Time From Onset, d: Malignant Lymphoma	Survival Time From Onset, d: Hemophagocytic Syndrome
Group 1			
1	Complete response	269	179
2	Partial response	692	2
3	Complete response	377	11
4	Partial response	1429	239
5	Progressive disease	69	12
6	Progressive disease	1063	133
7	Progressive disease	95	46
Group 2			
8	Progressive disease	2	2
9	Progressive disease	15	15
10	Progressive disease	51	51
11	Progressive disease	31	31
12	Progressive disease	31	31
13	Progressive disease	108	108
14	Progressive disease	159	159
15	Progressive disease	78	78
16	Progressive disease	14	14
17	Progressive disease	64	64
18	Progressive disease	3	3
19	Progressive disease	111	111
20	Progressive disease	34	34

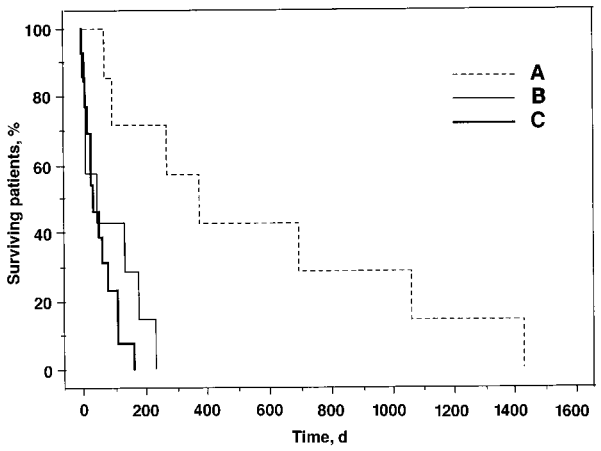

Figure 1. The survival curve of patients with T/natural killer–cell lymphoma–associated hemophagocytic syndrome (HPS), A, after the onset of lymphoma in group 1; B, after the onset of HPS in group 1; and C, after the onset of HPS in group 2. The survival curves of B and C are almost identical. The median survival time was 46 days in group 1 and 34 days in group 2 (P = .2511 by the log rank test).

Table 5.
Immunohistochemical and Genetic Features*

Case No.	CD2	cCD3	CD45RO	CD20	CD56	EBER	CM	Others	TCRr
Group 1									
1	+	+	ND	–	–	–	–	$CD4^+$	ND
2	ND	+	ND	–	–	–	–		ND
3	+	+	+	–	+	+	+		ND
4	+	+	+	–	+	+	+		ND
5	+	–	ND	–	+	+	+		G
6	ND	+	ND	–	–	+	+		ND
7	+	+	+	–	–	+	+		ND
Group 2									
8	+	+	+	–	–	–	+	$CD8^+$	ND
9	+	–	–	–	–	–	+	$CD8^+$	R
10	+	–	+	–	–	+	+		G
11	+	+	+	–	+	+	+		ND
12	–	+	+	–	+	+	+		ND
13	+	–	ND	–	+	+	NA		G
14	+	+	ND	–	–	+	+		ND
15	+	–	ND	–	–	+	+		G
16	ND	+	ND	–	+	–	+	$CD4^+$	ND
17	+	–	ND	–	+	–	+	$CD4^-8^-$	G
18	+	–	+	–	+	+	+		ND
19	+	+	+	–	+	+	+		ND
20	–	–	+	–	+	+	+		ND

*EBER indicates Epstein-Barr virus–encoded early RNAs; CM, cytotoxic molecule, ie, TIA-1 and/or granzyme B; TCR, T-cell receptor gene; ND, not done; G, germline; R, rearrangement; NA not available.

large T-cell lymphoma with pleomorphic morphology in group 2, and 2 cases of EBV^- $CD56^+$ NK/T-cell lymphoma in group 2.

4. Discussion

It is generally accepted that patients with T/NK-cell lymphoma develop HPS during their clinical course. However, the relationship between the histopathological subtypes of T/NK-cell lymphoma and HPS remains to be explained. Nevertheless, several pathological terms, eg, angioinvasive type, angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)-like, immunoblastic, MH-like, and hepatosinusoidal type were previously used in relatively short case summaries and isolated case reports [14].

We analyzed the clinicopathological features of 20 cases of T/NK-LAHS. The expression of CD56 and CM (TIA-1 and/or granzyme B) was observed at high prevalence (CD56, 11/20; CM, 17/19). EBV was also highly associated with T/NK-LAHS (14/20). T/NK-LAHS patients were clinically subdivided into 2 groups based on the onset of HPS [8]. However, the majority of cases (14 of 20, 70%), including 5 (79%) of 7 cases in group 1 and 9 (69%) of 13 in group 2, were categorized as nasal and nasal-type NK/T-cell lymphoma according to the WHO classification [12]. This type of tumor is more prevalent among Asians and most cases are highly aggressive, with extranodal presentation. The lesion reveals a polymorphous composition as well as a close association of EBV and the expression of CD56 and CMs in tumor cells. Su et al also reported that 15 (65%) of their 23 lymphoma cases in Taiwan, which had manifested HPS clinically, were of T-cell lineage with EBV association, although CD56 and CM were not described in their series [15]. The percentage was very similar to that of the present series (70%), suggesting that about two-thirds of the cases of T/NK-LAHS might be regarded as nasal and nasal-type NK/T-cell lymphoma.

Table 6.
Histopathological Diagnosis After Review*

Case No.	Histopathological Diagnosis
Group 1	
1	Peripheral T-cell lymphoma, unspecified, with plemorphic large cell morphology
2	Angioimmunoblastic T-cell lymphoma
3	Nasal NK/T-cell lymphoma
4	Nasal NK/T-cell lymphoma
5	Nasal NK/T-cell lymphoma
6	Nasal-type NK/T-cell lymphoma
7	Nasal NK/T-cell lymphoma
Group 2	
8	Cytotoxic large T-cell lymphoma with pleomorphic morphology and angiocentric pattern
9	Cytotoxic large T-cell lymphoma with pleomorphic morphology
10	Nasal-type NK/T-cell lymphoma
11	Nasal-type NK/T-cell lymphoma
12	Nasal-type NK/T-cell lymphoma
13	Nasal-type NK/T-cell lymphoma
14	Nasal-type NK/T-cell lymphoma
15	Nasal-type NK/T-cell lymphoma
16	$CD56^+$ NK/T-cell lymphoma, unspecified
17	$CD56^+$ NK/T-cell lymphoma, unspecified
18	Nasal NK/T-cell lymphoma
19	Nasal-type NK/T-cell lymphoma
20	Nasal-type NK/T-cell lymphoma

*NK indicates natural killer.

In our study, 4 cases (cases 11, 18, 19, and 20) in group 2 had the same common extranodal lesions as group 1, involving pulmonary, paranasal, and subcutaneous tissues, and their diagnoses were nasal and nasal-type NK/T-cell lymphoma. According to this data, it is possible that these group 2 cases were the same disease as the group 1 cases, but at a more aggressive stage.

The other 9 cases in group 2 did not show the typical extranodal lesions, even under careful examination. Five of the 9 cases showed nasal and nasal-type NK/T-cell lymphoma. Taken together, it appears quite feasible that these lymphomas were nasal and nasal-type NK/T-cell lymphomas originating from bone marrow, liver, and spleen.

CD56 expression among peripheral T/NK-cell lymphomas is relatively rare except for some extranodal entities in the forthcoming WHO schemes [13,16,17]. Recently, Macon et al reported 6 cases of $CD56^+$ PTCL, which featured marked hepatosplenomegaly without peripheral lymphadenopathy, $CD3^+CD8^+CD56^+$ phenotype, and anemia, thrombocytopenia, and lymphocytosis [18]. These lymphomas appear to be in the same continuous spectrum as group 2.

Although each patient's risk category based on the international prognostic index (IPI) [19] was variable, the prognosis was very poor in our study. The median survival time after the onset of HPS was only 1 to 2 months. The poor prognosis may be caused by the fact that nasal and nasal-type NK/T-cell lymphoma is resistant to standard chemotherapy [20,21]. Furthermore, uncontrollable HPS harasses multiorgan conditions throughout the clinical course in patients with T/NK-cell lymphoma. HPS may be one of the risk factors for T/NK-cell lymphoma, although further investigation is needed about differences in survival between T/NK-cell lymphoma with HPS and without HPS.

In conclusion, the histological subtypes of T/NK-cell lymphoma with HPS were predominantly nasal and nasal-type NK/T-cell lymphomas, regardless of the time of onset of HPS and which of the 2 groups the cases belonged to.

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