A distinct subtype of Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorder: adult patients with chronic active Epstein-Barr virus infection-like features

Keisuke Kawamoto,[1,2] Hiroaki Miyoshi,[1] Takaharu Suzuki,[1,2] Yasuji Kozai,[3] Koji Kato,[4] Masaharu Miyahara,[5] Toshiaki Yujiri,[6] Ilseung Choi,[7] Katsumichi Fujimaki,[8] Tsuyoshi Muta,[9] Masaaki Kume,[10] Sayaka Moriguchi,[11] Shinobu Tamura,[12] Takeharu Kato,[13] Hiroyuki Tagawa,[14] Junya Makiyama,[15] Yuji Kanisawa,[16] Yuya Sasaki,[1] Daisuke Kurita,[1] Kyohei Yamada,[1] Joji Shimono,[1] Hirohito Sone,[2] Jun Takizawa,[2] Masao Seto,[1] Hiroshi Kimura[17]* and Koichi Ohshima[1]*

[1]Department of Pathology, Kurume University School of Medicine; [2]Department of Hematology, Endocrinology and Metabolism, Faculty of Medicine, Niigata University; [3]Department of Hematology, Tokyo Metropolitan Tama Medical Center, Fuchu; [4]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka; [5]Department of Hematology, Karatsu Red Cross Hospital; [6]Third Department of Internal Medicine, Yamaguchi University School of Medicine, Ube; [7]Department of Hematology, National Hospital Organization Kyushu Cancer Center, Fukuoka; [8]Department of Hematology, Fujisawa City Hospital; [9]Department of Hematology, Japan Community Health Care Organization Kyushu Hospital; [10]Department of Hematology, Hiraka General Hospital, Yokote; [11]Department of Pathology, Miyazaki University; [12]Department of Hematology and Oncology, Wakayama Medical University; [13]Department of Hematology, Sasebo City General Hospital; [14]Department of Hematology, Nephrology, and Rheumatology, Akita University Graduate School of Medicine; [15]Department of Hematology, National Hospital Organization Nagasaki Medical Center, Omura; [16]Department of Hematology and Oncology, Oji General Hospital, Tomakomai and [17]Department of Virology, Faculty of Medicine, Nagoya University, Japan

**HK and KO share senior authorship.*

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Correspondence: miyoshi_hiroaki@med.kurume-u.ac.jp

Supplemental Appendix

Title：A distinct subtype of Epstein Barr virus positive T/NK-cell lymphoproliferative disorder: Adult patients with chronic active Epstein Barr virus infection-like features

Contents

[Abbreviations]

CAEBV: Chronic active EBV infection, EBNA: Epstein–Barr virus nuclear antigen 1, EBV: Eptein-Barr virus, HPS: Hemophagocytic syndrome, HSCT: hematopoietic stem cell transplantation, OS: Overall survival, ENKTL: Extranodal NK/T cell lymphoma, nasal type

[Methods]

EBV-DNA viral load in peripheral blood

Peripheral blood sample was obtained from each patient at diagnosis, in order to investigate the viral load by real-time quantitative polymerase chain reaction (qPCR). A positive result was defined as an EBV-DNA viral load of ≥200 copies/ml, as previously reported.[1]

Southern blot hybridization

The clonality of EBV was determined by Southern blot, using a terminal repeat probe as previously described.[2,3]

TCR gamma gene rearrangement

T-cell receptor (TCR) gamma gene rearrangement was determined by multiplex PCR using the T-cell Gene Rearrangement/Clonality assay, which was manufactured in house, and standardized according to the European BIOMED -2 collaborative study.[4,5]

In situ hybridization for Epstein-Barr virus-encoded RNA (EBER)

EBV was detected by in situ hybridization (ISH) with a fluorescein-conjugated EBV peptide nucleic acid probe kit (DakoCytomation, Glostrup, Denmark) following institutional procedures.[5]

Histology and Immunophenotype

Specimens were subjected to immunohistochemistry (IHC) preparation as follows: sections from formalin-fixed, paraffin-embedded blocks were stained with hematoxylin-eosin. According to a previous report on histological classification[6], we categorized the patients into 3 groups (A1, A2, and A3; criteria shown in the legend of Figure S1). At initial diagnosis, the raw biopsied specimens at the initial diagnosis were used for flow cytometry (FCM) to investigate the immunophenotype in addition to IHC. Primary antibodies used for IHC and FCM are described in Table S1. Pathological images are demonstrated in Figure S1.

Determination of EBV-infected cell type

To determine which cells were infected with EBV, we analyzed the expression of cluster of differentiation (CD)2, cytoplasmic CD3 (cCD3), surface CD3 (sCD3), CD7, CD16, and CD56 on EBV-infected cells in the biopsied specimens by FCM or IHC according to the institutional procedures.[7] In this study, the phenotype of NK-cell type was defined as being positive for CD2, cCD3, CD7 and CD16, and negative for sCD3 as previous reported.[8] T-cells were defined as being sCD3 positive, thereby excluding NK-cells. The pathological images are also shown in Figure S1.

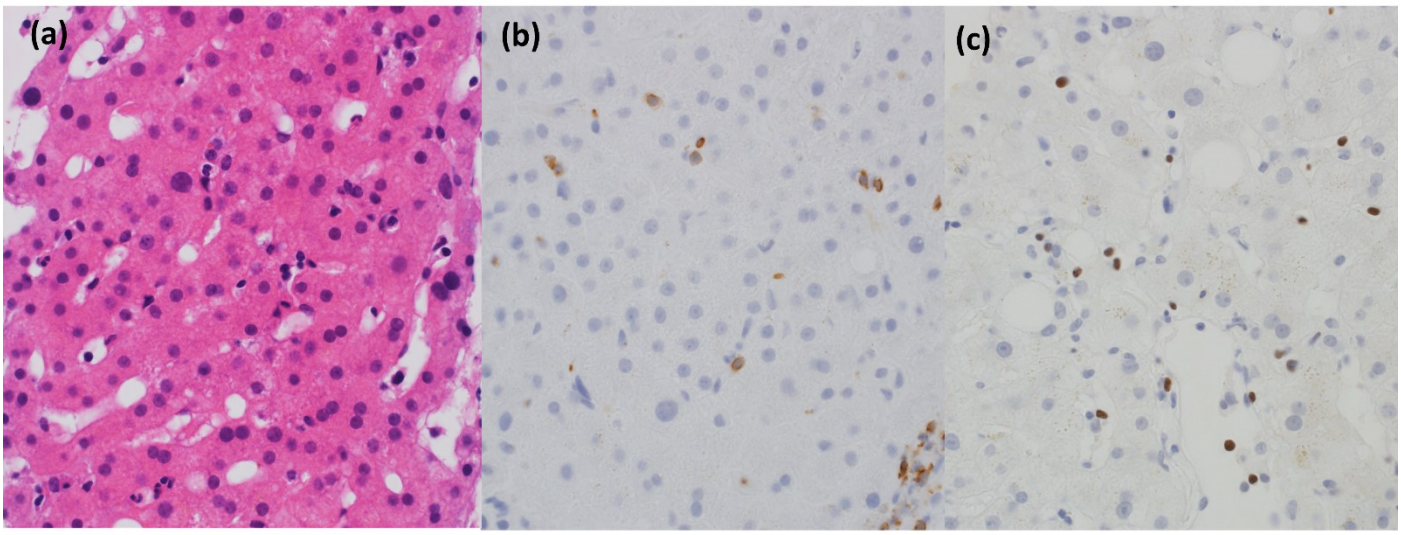
Statistical analysis

Clinical features of all patients were compared by chi-square, Fisher's exact, and Mann-Whitney U-tests. Overall survival (OS) was defined as the time from the day of diagnosis to the day of death or last follow-up. Kaplan-Meier estimates were used to predict OS, which were compared by using log-rank tests. All calculated *P*-values were two-tailed, and those <0.05 were considered statistically significant. All statistical analyses were performed on EZR.[9]

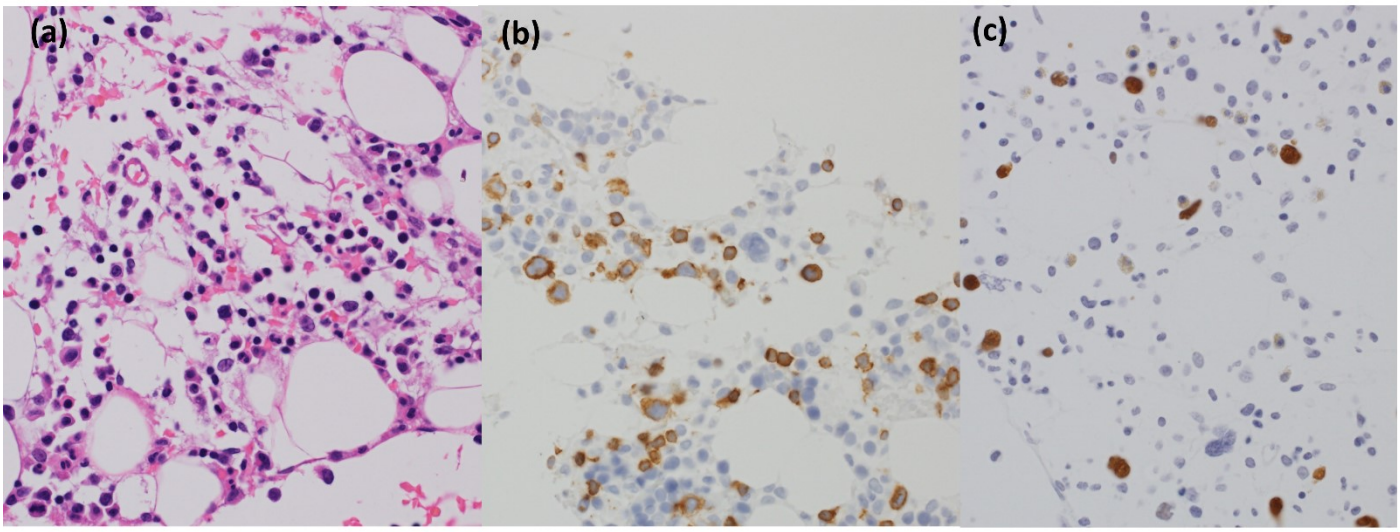
Figure S1. Pathological images according to the histological categorization.

NOTE: Histological categorization, which was supposed by K. Ohshima et al.[6], was based on pathological evaluation as follows: (i) Category A1, polymorphic without clonal proliferation of EBV-infected cells; (ii) Category A2, polymorphic lymphoproliferative disorder (LPD); (iii) Category A3, monomorphic LPD.

(1) Category A1 (a: Hematoxylin and Eosin (HE) staining, b: CD3, c: EBER)



(2) Category A2 (a: HE staining, b: CD3, c: EBER)



(3) Category A3 (a: HE staining, b: CD3, c: EBER)

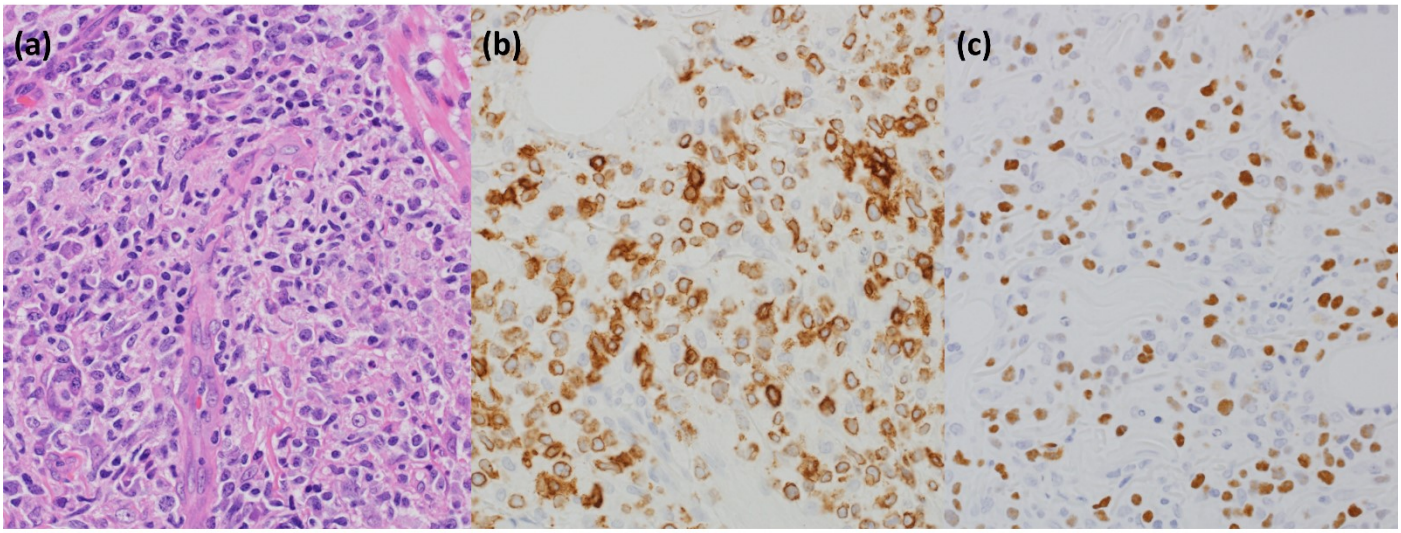


Figure S2. The distribution of onset age in adult-onset CAEBV. Onset of CAEBV was observed in all ages. Median age at diagnosis was 39 years (range 16-86 years).

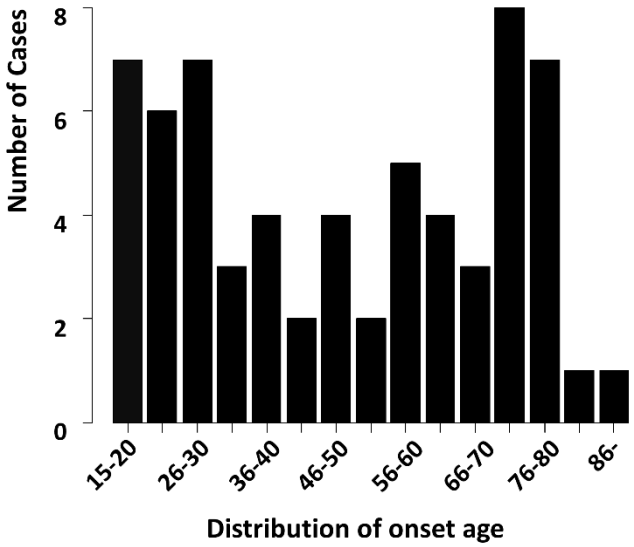
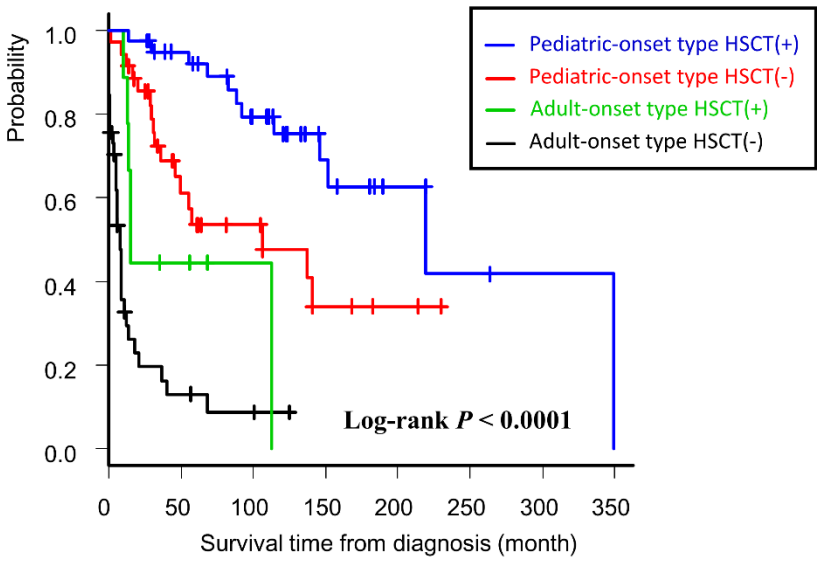


Figure S3. Comparison of overall survival between adult-onset and pediatric-onset CAEBV patients. Even if we compared the prognosis with regard to the presence or absence of allogeneic HSCT since HSCT was suggested to be an independent prognostic factor, significant differences in prognosis were observed between adult-onset and pediatric-onset CAEBV (Log-rank $P < 0.0001$).



Patient at risk

Pediatric-onset type HSCT(+)	45	4	2	0	0	0	0	0
Pediatric-onset type HSCT(-)	9	3	1	0	0	0	0	0
Adult-onset type HSCT(+)	35	16	10	4	2	0	0	0
Adult-onset type HSCT(-)	40	33	22	11	4	2	1	0

Figure S4. Comparison of overall survival between ≥50 years old and < 50 years old patients. There was no difference in overall survival among the two groups of ≥50 years old and < 50 years old patients. ($P = 0.922$)

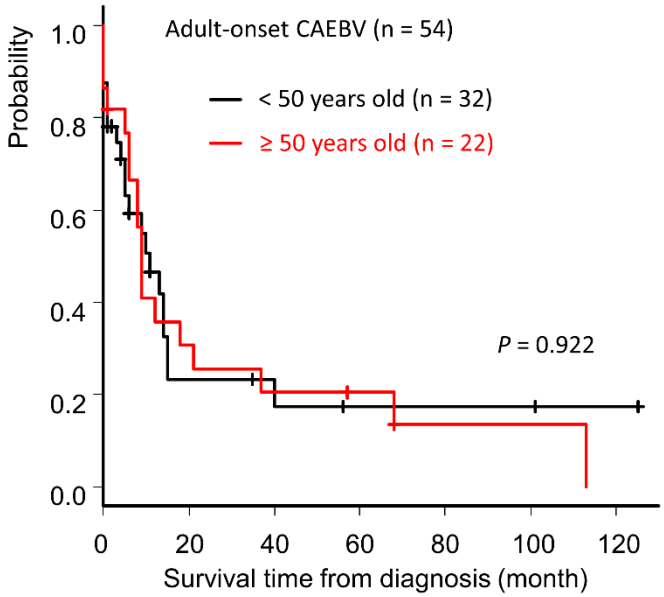


Figure S5. Comparison of adult patients with CAEBV and Nodal PTCL-NOS (EBV+). There was no difference in overall survival among the two groups of adult patients with CAEBV and Nodal PTCL-NOS (EBV+). ($P = 0.143$)

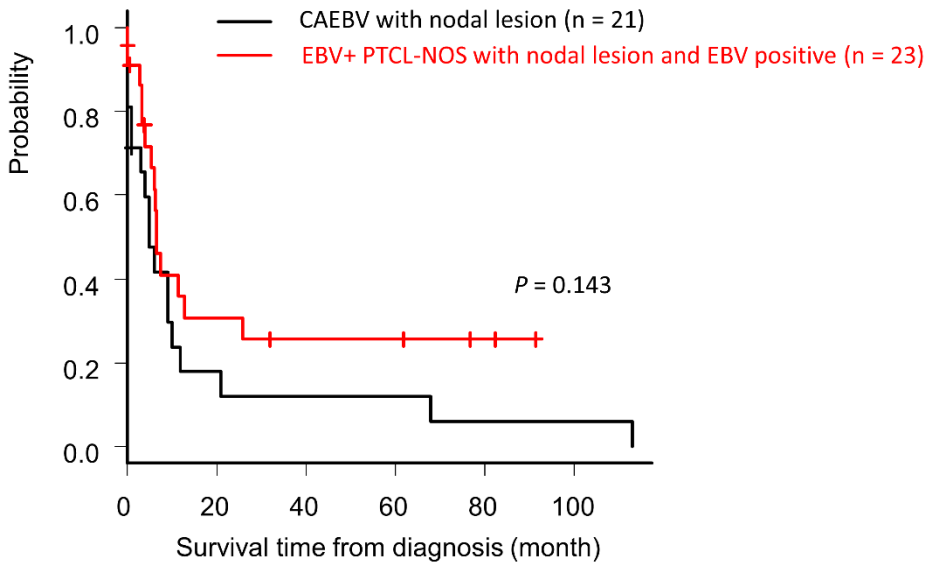


Table S1. Primary antibodies for immunohistochemistry (IHC) and flow cytometry (FCM).

Table S1. Primary antibodies for immunohistochemistry and flow cytometry		
Antigen	**Clone**	**Brand**
Immunohistochemistry		
CD3	F7.2.38	DakoCytomation
CD4	SP35	Ventana Medical Systems
CD7	3A1	Beckman Coulter
CD8	C8/144B	DakoCytomation
CD20	L26	DakoCytomation
CD56	N901	Beckman Coulter
TIA-1	2G9A10F5	Beckman Coulter
Granzyme B	GRB-7	Chemicon Temecula
Flow cytometry		
CD2	SFCI3Pt2H9(T11)	Beckman Coulter
CD3	UCHT1	Beckman Coulter
CD7	3A1(3A1E-12H7)	Beckman Coulter
CD16	3G8	Beckman Coulter
CD19	B4:89B	Beckman Coulter
CD20	L27	BD Biosciences
CD56	NHK-1:N908	Beckman Coulter

Table S2. Clinical characteristics of adult-onset patients with nodal and extranodal lesion

Table S2. Clinical characteristics of adult-onset patients with nodal and extranodal lesions			
Patient characteristics	**Localization**		***P*** [§]
	Nodal type (n = 21)	**Extranodal type** (n = 33)	
Sex			
Male, n (%)/Female, n (%)	12 (57.1)/9 (42.9)	19 (57.6)/14 (42.4)	1
Median age, y (range)	49 (16-86)	39 (19-78)	0.929
≥ 50 years old	10	12	0.571
Past medical history			
Hypersensitivity to mosquito bites, n (%)	1 (4.8)	3 (9.1)	1
Hydroa vacciniforme, n (%)	0 (0)	2 (6.1)	0.516
ECOG PS High (2-4), n (%)	9 (42.9)	8 (24.2)	0.229
Laboratory test at initial diagnosis			
Anemia (Hb <10.5 g/dL), n (%)	6 (28.6)	9 (27.3)	1
Thrombocytepenia (< 100×10^9/L), n (%)	9 (42.9)	19 (57.6)	0.403
LDH elevation, n (%)	14 (66.7)	26 (78.8)	0.355
Transaminase, elevation, n (%)	10 (47.6)	12 (36.4)	0.571
Hemophagocytic syndrome, n (%)	10 (47.6)	15 (45.5)	1
EBV-related antibody			
VCA-IgG, median titer (range)	160 (40-1280)	160 (10-5120)	
VCA-IgM, median titer (range)	<10 (<10-20)	<10 (<10-60)	na
EBNA, median titer (range)	20 (<10-40)	10 (<10-320)	
Unknown, n (%)	6 (28.6)	7 (21.2)	
EBV-DNA, in plasma (copy/mL)			
Median (range)	1×10^4(nd-1×10^6)	3.4×10^4(2.6×10^2-7.3×10^4)	na
Unknown, n (%)	8 (53.8)	9 (46.2)	
EBV monoclonality by Southern blot, n (%)	3/4 (75.0)	5/5 (100)	na
EBER$^+$cell counts /HPF, median (range)	58 (2-435)	168 (15-487)	0.308
Histological classification[ref:9]			
A1, n (%)	3 (60.0)	2 (40.0)	
A2, n (%)	3 (42.9)	4 (57.1)	0.864
A3, n (%)	4 (40.0)	6 (60.0)	
Immunophenotype			
CD4	7 (70.0)	3 (30.0)	na

CD8	4 (40.0)	6 (60.0)	na
CD56	5 (50.0)	5 (50.0)	na
TCRab (n = 8)	6/8 (75.0)	na	na
Allogeneic HSCT	1 (50.0)	1 (50.0)	na

CAEBV: Chronic active EBV infection, EBV: Eptein-Barr virus, EBNA: Epstein–Barr virus nuclear antigen 1, EBV-DNA: EBV-Deoxyribonucleic acid, ECOG PS: Eastern Cooperative Oncology Group Performance status, EBER: Epstein-Barr virus-encoded RNA (EBER), nd: not detected (EBV-DNA < 2×10^2 copies/mL), HPF: high power field, HSCT: hematopoietic stem cell transplantation, * indicates statistically significant, na: not avalilable, $P^{\S}$: Nodal vs Extranodal type

Table S3. Clinical features of all 75 cases with pediatric-onset CAEBV from the previous report.[10]

No	Sex	Age at onset(yr)	Age at diagnosis (yr)	EBV-DNA log (copies) at diagnosis		Mainly EBV infected cells	Clonality at diagnosis		Chemotherapy	HSCT	Final outcome	Cause of death	Period from onset (mo)
				MNC (/μg DNA)	Plasma (/mL)		EBV terminal repeat	TCR rearrangement					
1	M	9	11	4.3	2.9	T	mono	n.t.	no	no	dead	hepatic failure	29
2	M	7	12	3.5	n.t.	T	mono	n.t.	yes	yes	alive/CR		184+
3	M	3	6	3.5	2.8	T	mono	n.t.	no	no	dead	sepsis	36
4	M	5	10	4.9	n.t.	T	mono	n.t.	yes	yes	alive/CR		189+
5	F	2	14	4.8	4.2	NK	mono	no	no	yes	dead	sepsis, ICH	152
6	M	9	13	3.5	0.3	NK	mono	β	yes	yes	alive/CR		114+
7	F	1	1	5.4	8.4	T	und.	β	yes	no	alive/CR		62+
8	M	2	16	4.4	4.6	NK	mono	β	yes	yes	dead	TMA, intestinal bleeding	219
9	M	13	18	4.5	2.0	T	mono	γ	yes	no	alive/PR		183+
10	F	9	14	4.7	n.t.	NK	mono	n.t.	no	no	dead	esophagus perforation	58
11	F	4	12	4.0	und.	NK	mono	no	no	no	alive/CR		230+
13	M	4	6	3.5	3.0	T	und.	no	yes	yes	dead	TMA, ICH	114
14	F	14	19	4.7	4.2	T	mono	β	yes	yes	dead	TMA, ICH	55
15	M	1	6	4.2	3.5	T	mono	n.t.	no	yes	alive/CR		190+
16	F	10	12	5.0	4.5	T	oligo	β	yes	no	dead	MOF	31
18	F	6	7	4.6	4.2	NK	mono	n.t.	yes	yes	alive/CR		136+
19	M	8	18	4.7	und.	NK	mono	n.t.	yes	yes	dead	sepsis, MOF	92
20	M	3	5	4.8	3.6	NK	mono	n.t.	yes	yes	dead	TMA, renal failure	88
21	F	8	9	3.6	3.0	T	poly	β	yes	no	dead	MOF	50
22	M	8	10	3.8	3.6	T	mono	no	yes	no	dead	hepatic failure	32

23	M	6	7	4.2	2.8	T	n.t.	β	no	no	dead	heart failure	46
25	M	12	17	3.8	und.	NK	mono	n.t.	yes	yes	alive/CR		190+
26	M	9	15	4.6	4.1	NK	mono	n.t.	no	yes	alive/CR		123+
27	F	13	19	4.5	3.1	NK	oligo	no	no	yes	alive/CR		219+
28	F	3	31	4.8	4.6	NK	mono	n.t.	yes	yes	dead	DIC	349
30	F	11	13	4.2	3.1	T	mono	γ	yes	no	dead	intestinal perforation	20
31	M	5	11	5.1	3.2	NK	poly	n.t.	no	yes	alive/CR		158+
32	M	3	8	4.0	3.6	NK	mono	n.t.	yes	yes	alive/CR		181+
33	M	1	1	2.6	und.	T	mono	β	yes	yes	alive/CR		121+
35	M	11	16	4.5	und.	NK	mono	no	no	yes	alive/CR		145+
36	M	5	10	3.3	und.	T	mono	γ,δ	no	no	alive/SD		168+
37	F	7	10	2.0	und.	NK	und.	no	no	no	alive/SD		107+
38	M	1	1	3.2	2.0	T	mono	no	yes	no	dead	heart failure	12
42	F	10	14	5.1	4.6	NK	oligo	no	yes	no	dead	sepsis	55
43	F	11	13	5.3	5.3	NK	oligo	no	yes	no	dead	pulmonary failure	29
47	M	4	4	4.9	3.3	NK	mono	no	yes	yes	alive/CR		100+
49	F	4	10	3.7	4.0	NK	mono	no	no	no	dead	MOF	106
50	F	2	3	4.0	3.1	NK	oligo	β,γ,δ	no	yes	alive/PR		110+
51	F	13	23	4.0	4.0	T	mono	β	no	yes	dead	cardiac failure	146
52	F	6	17	2.9	4.5	T	n.t.	β	yes	no	alive/SD		105+
53	M	9	27	3.6	3.0	NK	mono	no	yes	yes	alive/CR		263+
54	F	7	16	2.4	2.7	NK	n.t.	no	no	no	dead	cardiac failure	137
56	F	14	14	2.9	5.7	T	mono	no	yes	no	dead	MOF	9
57	F	5	7	5.5	6.0	T	mono	β	yes	no	dead	pulmonary edema	17
58	M	4	9	4.8	3.2	NK	mono	no	no	no	alive/SD		141+
59	F	1	1	5.9	2.3	T	mono	β	no	yes	alive/CR		82+
64	F	5	5	3.1	3.5	T	n.t.	no	no	no	alive/CR		61+
65	F	11	11	4.2	4.3	T	n.t.	β	yes	yes	dead	sepsis, ICH	29

67	F	2	7	4.8	4.2	NK	mono	no	yes	yes	alive/CR		110+
68	M	5	11	4.8	5.4	T	mono	no	yes	yes	alive/CR		124+
70	M	3	3	5.4	4.7	T	n.t.	β	yes	yes	alive/CR		43+
71	M	3	5	5.6	2.0	T	mono	δ	no	no	alive/SD		64+
73	M	5	10	5.0	3.0	T	mono	γ,δ	no	no	alive/SD		214+
74	M	1	1	4.7	3.5	NK	n.t.	no	no	no	alive/CR		34+
76	M	13	20	3.8	4.5	T	poly	γ	yes	yes	alive/SD		133+
77	F	10	16	4.7	5.0	T	n.t.	δ	no	yes	dead	GVHD, cardiac failure	83
78	M	7	9	5.4	4.9	NK	n.t.	no	yes	yes	alive/CR		62+
79	M	8	8	4.2	4.4	NK	n.t.	no	yes	no	alive/CR		44+
81	F	10	11	4.8	6.1	NK	mono	γ	yes	yes	dead	ICH	14
82	F	13	13	2.9	2.9	T	und.	no	no	yes	alive/CR		39+
84	F	13	18	5.0	3.7	T	mono	no	yes	yes	alive/CR		98+
86	M	6	8	3.0	n.t.	NK	n.t.	no	no	no	alive/CR		45+
87	F	2	2	3.7	3.1	T	oligo	no	yes	no	alive/CR		27+
88	F	1	1	3.6	4.5	T	n.t.	β,γ	yes	no	alive/PR		25+
89	M	1	1	5.3	n.t.	T	mono	β	no	no	dead	HPS	2
90	M	3	3	2.7	3.5	T	n.t.	γ	yes	yes	alive/CR		26+
92	M	7	8	5.2	4.1	NK	mono	β	no	yes	alive/CR		32+
96	F	9	10	4.8	4.0	T	mono	β	no	yes	alive/CR		28+
97	M	6	12	4.8	5.0	T	mono	β,γ,δ	no	no	alive/SD		81+
102	M	10	15	5.8	5.3	NK	mono	no	yes	yes	dead	MOF	68
103	M	1	3	6.1	4.2	NK	mono	no	yes	yes	alive/CR		59+
105	F	5	5	5.2	und.	T	oligo	β,γ,δ	no	no	alive/SD		18+
106	F	1	1	2.8	3.0	T	n.t.	no	yes	no	alive/CR		13+

NOTE: und: undetectable

Table S4. The clinical features of 82 patients with nodal type and extra-nodal type ENKTL.

Table S4. Patient characteristics of 82 patients with ENKTL

Patient characteristics	All patients n = 82
Sex	
Male, No. (%)	52 (62.9)
Female, No. (%)	30 (37.1)
Age (y), median (range)	55 (3-89)
≥ 61, No. (%)	48 (58.5)
< 61, No. (%)	34 (41.5)
ECOG Performance Status	
Low (0-1), No. (%)	64 (78.0)
High (2-4), No. (%)	18 (22.0)
B symptoms	
Abscence, No. (%)	43 (52.4)
Presence, No. (%)	39 (47.6)
Serum lactate dehydrogenase	
Normal, No. (%)	28 (34.1)
Elevated, No. (%)	54 (65.9)
Nasal type	
Yes, No. (%)	37 (45.1)
No, No. (%)	45 (54.9)
Lymph node involvement	
None or Regional, No. (%)	57 (69.5)
Distant, No. (%)	17 (20.7)
Unknown, No. (%)	8 (9.8)
Extra nodal sites	
< 2, No. (%)	50 (61.0)
≥ 2, No. (%)	34 (39.0)
Ann-Arbor	
Stage I/II, No. (%)	41 (50.0)
Stage III/IV, No. (%)	41 (50.0)
Hemophagocytic syndrome	
Abscence, No. (%)	62 (75.6)

Presence, No. (%)	20 (24.4)
IPI risk group	
Low (0-1), No. (%)	30 (36.1)
High (2-4), No. (%)	52 (15.5)
PINK risk group	
Low (0), No. (%)	6 (6.2)
Intermediate (1), No. (%)	36 (45.4)
High (2-4), No. (%)	40 (48.4)
EBV-DNA in whole blood	
Undetectable, No. (%)	5 (7.3)
Detectable, No. (%)	34 (41.5)
Unknown, No. (%)	43 (51.2)
Immunophenotype	
NK-cell type, No. (%)	67 (81.7)
T-cell type, No. (%)	15 (18.3)
Initial therapy response	
Complete response, n (%)	33 (40.2)
Partial response, No. (%)	19 (23.1)
Stable disease, No. (%)	4 (4.9)
Progressive disease, No. (%)	20 (24.4)
Best Supportive Care, No. (%)	2 (2.5)
Unknown, n (%)	4 (4.9)

LDH: lactate dehydrogenase, IPI: International Prognostic Index, NA: Not available

Table S5. Patient characteristics of ANKL and PTCL-NOS (Cytotoxic type and EBV positive)

Table S5. Patient characteristics of ANKL and PTCL-NOS (Cytotoxic+, EBV+)

Patient characteristics	ANKL n = 7	PTCL-NOS (Cytotoxic+, EBV+) n = 26
Sex		
Male, n (%)	5	13
Female, n (%)	2	13
Age (y), median (range)	62 (32-67)	68 (22-79)
≥ 61, n (%)	4	19
< 61, n (%)	3	7
Overall survival, Median month (range)	6 (0-103)	6.2 (0-91)

Table S6. Estimated onset age in 54 patients with adult-onset CAEBV.

Table S6. Estimated onset in 54 patients with adult onset chronic active EBV infection.

No.	Age at diagnosis	Sex	Estimated onset (prior to diagnosis)
1	70	F	2 years
2	78	F	3-6 months
3	36	F	6 months
4	62	M	2.5 years
5	19	F	2 years
6	48	M	6 months
7	24	F	> 1 year
8	16	F	1 year
9	86	F	1 year
10	59	M	7 months
11	69	M	4 years
12	41	M	> 6 months
13	18	M	2-3 years
14	71	F	> 3 months
15	49	M	> 6 months
16	78	M	1 year
17	23	M	> 3 years
18	21	M	> 5 years
19	71	M	> 6 months
20	52	F	> 1 year
21	39	F	2 years
22	73	M	3-6 months
23	78	F	> 1 year
24	62	F	> 1 year
25	25	M	3 years
26	75	M	3-6 months
27	19	M	2 years

28	36	M	4-5 months
29	46	M	> 1 year
30	48	M	3 years
31	29	M	8 years
32	42	F	3-4 months
33	29	F	6-12 months
34	37	M	> 3 years
35	28	M	1 year
36	27	M	> 1 year
37	19	M	> 1 year
38	23	F	> 5 years
39	30	M	> 1 year
40	20	F	> 1 year
41	28	F	3 months
42	26	F	8 years
43	23	F	6 years
44	76	M	3-6 months
45	71	M	> 3 months
46	57	M	6 years
47	58	F	1 year
48	19	F	6-12 months
49	35	M	3 months
50	65	M	> 1 year
51	76	F	6 months
52	78	M	> 1 year
53	33	M	> 10 years
54	58	F	> 10 years

Table S7. EBV status and clonality assay in 54 patients with adult-onset CAEBV.

Table S7. EBV status and clonality assay in 54 patients with adult-onset CAEBV									
No.	Age at diagnosis	Sex	EBV-related antibody			EBV-DNA in Plasma (copy/mL)	Clonality		EBV-positive cell counts/HPF
			VCA IgG	VCA IgM	EBNA		TCRGR	EBV-Southern	
1	70	F	160	< 10	< 10	400	na	na	159
2	78	F	640	< 10	40	300	na	na	168
3	36	F	80	< 10	10	1000	na	na	102
4	62	M	160	< 10	10	200000	positive	na	51
5	19	F	1280	40	< 10	140000	positive	na	na
6	48	M	640	60	320	10000	negative	na	25
7	24	F	160	< 10	20	370000	negative	na	49
8	16	F	1280	< 10	40	7000	negative	na	386
9	86	F	80	< 10	10	na	positive	na	42
10	59	M	160	< 10	10	na	positive	na	na
11	69	M	na	na	na	1100	na	mono	68
12	41	M	160	< 10	10	na	na	mono	65
13	18	M	na	na	na	10000	negative	mono	33
14	71	F	na	na	na	na	positive	mono	62
15	49	M	80	< 10	10	200	positive	na	12
16	78	M	na	na	na	na	negative	mono	218
17	23	M	320	< 10	40	2000	na	na	36
18	21	M	160	< 10	10	260	negative	mono	3
19	71	M	5120	10	40	1700	na	na	15
20	52	F	80	< 10	10	73000	na	mono	na
21	39	F	2560	< 10	20	41000	negative	na	12
22	73	M	640	< 10	40	negative	na	na	61
23	78	F	na	na	na	na	negative	na	156
24	62	F	320	10	20	na	na	na	68
25	25	M	1280	< 10	20	1500	negative	na	36
26	75	M	na	na	na	na	na	na	178
27	19	M	640	< 10	< 10	2800	positive	mono	2
28	36	M	160	< 10	40	50000	negative	mono	53

29	46	M	160	< 10	10	34000	negative	mono	33
30	48	M	160	< 10	10	4000	negative	mono	28
31	29	M	160	< 10	40	20000	negative	mono	4
32	42	F	320	< 10	10	100000	negative	mono	10
33	29	F	2560	< 10	80	65000	positive	mono	23
34	37	M	na	na	na	na	na	mono	3
35	28	M	10	< 10	10	37000	positive	poly	3
36	27	M	40	20	20	600000	positive	poly	13
37	19	M	40	20	< 10	30000	positive	na	237
38	23	F	160	< 10	10	2000	positive	mono	412
39	30	M	160	< 10	< 10	120000	positive	mono	7
40	20	F	40	20	< 10	6600	positive	poly	11
41	28	F	na	na	na	660	negative	mono	96
42	26	F	40	< 10	20	900	negative	poly	13
43	23	F	320	< 10	10	300	negative	mono	214
44	76	M	na	na	na	na	negative	mono	325
45	71	M	na	na	na	na	positive	mono	87
46	57	M	160	< 10	80	na	negative	mono	487
47	58	F	1280	10	40	na	na	mono	347
48	19	F	80	< 10	10	1100000	na	mono	16
49	35	M	160	< 10	10	na	negative	na	11
50	65	M	640	< 10	20	na	na	na	435
51	76	F	na	na	na	na	na	na	322
52	78	M	na	na	na	50000	na	na	2
53	33	M	na	na	na	na	na	mono	232
54	58	F	160	< 10	10	1000000	positive	poly	58

na: not available, TCRGR: T-cell receptor gamma rearrangement, mono: monoclonal pattern, poly: polyclonal pattern, HPF: high power field

Table S8. EBV-infected cell type and histological classification[6] in 54 patients with adult onset CAEBV.

Table S8. EBV-infected cell type and histological classification in 54 patients with adult-onset chronic active EBV infection and EBV-T/NK-LPD

No.	Age at diagnosis	Sex	Infected cell type	Histological clasiffication
1	70	F	NK	A2
2	78	F	NK	A3
3	36	F	NK	A3
4	62	M	T	A1
5	19	F	T	A1
6	48	M	NK	A1
7	24	F	NK	A2
8	16	F	NK	A3
9	86	F	T	A3
10	59	M	T	A2
11	69	M	NK	A3
12	41	M	NK	A2
13	18	M	NK	A3
14	71	F	T	A3
15	49	M	T	A1
16	78	M	NK	A3
17	23	M	NK	A1
18	21	M	NK	A2
19	71	M	NK	A2
20	52	F	NK	A2
21	39	F	NK	A2
22	73	M	NK	A1
23	78	F	NK	A1
24	62	F	T	A2
25	25	M	NK	A2
26	75	M	NK	A3
27	19	M	T	A3
28	36	M	NK	A2
29	46	M	NK	A2

30	48	M	NK	A2
31	29	M	NK	A3
32	42	F	NK	A2
33	29	F	T	A2
34	37	M	T	A2
35	28	M	T	A1
36	27	M	T	A1
37	19	M	T	A3
38	23	F	T	A1
39	30	M	T	A1
40	20	F	T	A1
41	28	F	NK	A3
42	26	F	NK	A1
43	23	F	NK	A1
44	76	M	NK	A3
45	71	M	T	A3
46	57	M	NK	A2
47	58	F	T	A2
48	19	F	T	A2
49	35	M	NK	A2
50	65	M	T	A3
51	76	F	NK	A3
52	78	M	T	A1
53	33	M	NK	A3
54	58	F	T	A1

Table S9. Treatment and outcome in 54 patients with adult-onset CAEBV.

Table S9. Treatment and outcome in 54 patients with adult-onset chronic active EBV infection.						
No.	Age at diagnosis	Sex	Chemotherapy	Allo-HSCT	Survival (month)	Outcome
1	70	F	SMILE	no	37	Dead
2	78	F	SMILE	no	21	Dead
3	36	F	CHOEP, SMILE	done	56	Alive
4	62	M	SMILE	no	0	Dead
5	19	F	None	done	35	Alive
6	48	M	DEX+CPA+ETP	no	1	Dead
7	24	F	Unknown	no	11	Alive
8	16	F	CHOP, SMILE	no	0	Dead
9	86	F	Observation	no	12	Dead
10	59	M	CHOP, EPOCH, CHASE, VP16	done	113	Dead
11	69	M	Unknown	no	18	Dead
12	41	M	observation	no	101	Alive
13	18	M	Unknown	no	1	Alive
14	71	F	THP-COP	no	9	Dead
15	49	M	CHOP, CHASE	no	5	Dead
16	78	M	CHOP	no	9	Dead
17	23	M	CHOP	no	1	Dead
18	21	M	PSL	no	4	Alive
19	71	M	PSL, mPSL	no	0	Dead
20	52	F	None	done	68	Alive
21	39	F	CHOP	no	40	Dead
22	73	M	THP-COP, EPOCH	no	6	Dead
23	78	F	CHOP	no	57	Alive
24	62	F	THP-COP	no	0	Dead
25	25	M	DeVIC	no	4	Alive
26	75	M	PSL	no	1	Dead
27	19	M	CHOP	no	9	Dead
28	36	M	PSL+VP-16	no	0	Dead
29	46	M	CSP+PSL+ETP、CHOP	no	14	Dead

30	48	M	CHOP, CHASE, IVAC	done	10	Dead
31	29	M	mPSL, DEX+CPA+ETP, CyA	done	15	Dead
32	42	F	mPSL	no	5	Dead
33	29	F	DEX+CPA+ETP, CHOP	no	6	Alive
34	37	M	PSL	no	1	Dead
35	28	M	ETP, CHOP, AraC	no	11	Dead
36	27	M	mPSL	no	0	Dead
37	19	M	mPSL, DEX+CPA+ETP, CyA	no	0	Dead
38	23	F	PSL	no	125	Alive
39	30	M	mPSL	done	14	Dead
40	20	F	mPSL, DEX+CPA+ETP, CyA	no	2	Alive
41	28	F	CHOP	no	3	Dead
42	26	F	CHASE	done	15	Dead
43	23	F	THP-COP, ESHAP	done	13	Dead
44	76	M	DeVIC	no	8	Dead
45	71	M	CHOP, DeVIC	no	68	Dead
46	57	M	DEVIC	no	8	Dead
47	58	F	DeVIC	no	6	Dead
48	19	F	VP-16	no	4	Dead
49	35	M	DEX+CPA+ETP	no	6	Dead
50	65	M	DeVIC	no	5	Dead
51	76	F	Unknown	no	1	Alive
52	78	M	Unknown	no	9	Dead
53	33	M	PSL	no	1	Alive
54	58	F	Observation	no	1	Alive

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