Cutaneous angioimmunoblastic T-cell lymphoma: Epstein-Barr virus positivity and its effects on clinicopathologic features

Woo Jin Lee, MD, PhD, PhD, Kwang Hee Won, MD, Jae Won Choi, MD, Chong Hyun Won, MD, PhD, Sung Eun Chang, MD, PhD, Jee Ho Choi, MD, PhD, and Mi Woo Lee, MD, PhD
Seoul, Korea

Background: Epstein-Barr virus (EBV) positivity frequently presents in patients with nodal angioimmunoblastic T-cell lymphoma (AITL). However, the presence of EBV in skin lesions and its clinicopathologic significance have not been evaluated.

Objective: To analyze the clinical and histopathologic features of cutaneous AITL and evaluate EBV positivity in skin tissue and its effects on clinicopathologic features of AITL.

Methods: Clinicopathologic variables in patients with cutaneous AITL were analyzed and compared depending on EBV in situ hybridization status in skin lesions by using patients' medical records.

Results: Of the 86 patients with AITL, 42 had a cutaneous presentation. In situ hybridizations positive for EBV were noted in 19 of 42 patients with cutaneous AITL. EBV positivity was more common in papular and nodular skin lesions than other cutaneous morphologies, such as nonspecific rash or purpuric patches. An EBV-positive in situ hybridization was associated with a pattern of dense, superficial and deep infiltrates of pleomorphic, large-sized, atypical lymphocytes. EBV positivity in skin lesions was an independent negative prognostic factor in patients with AITL.

Limitations: Retrospective study at a single institution.

Conclusion: EBV-positive cutaneous AITL is associated with distinctive clinicopathologic features. (J Am Acad Dermatol 2019;81:989-97.)

Key words: angioimmunoblastic T-cell lymphoma; Epstein-Barr virus; outcome; prognostic factor; skin; survival.

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive lymphoid malignancy accounting for 15%-20% of peripheral T-cell lymphomas.[1] AITL is typically diagnosed by lymph node (LN) biopsy and is regarded as a systemic disorder presenting with constitutional symptoms, B symptoms (fever, night sweats, and weight loss), generalized lymphadenopathy, hepatosplenomegaly, anemia, polyclonal hypergammaglobulinemia,

Abbreviations used:

AITL:	angioimmunoblastic T-cell lymphoma
BCL-6:	B-cell lymphoma 6 protein
EBV:	Epstein-Barr virus
LDH:	lactate dehydrogenase
LN:	lymph node
OS:	overall survival
PD-1:	programmed cell death protein 1
T_{FH}:	follicular helper T cell

From the Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul.
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Correspondence to: Mi Woo Lee, MD, PhD, Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, 43 Olympic-ro, Songpa-gu, 138-736, Seoul, Korea. E-mail: jijulee@hanmail.net.
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and skin rash.[2] AITL tumor cells in LNs express several follicular helper T cell (T_{FH}) markers and are often outnumbered by reactive T cells. For diagnostic purposes, CXC motif chemokine 13, programmed cell death protein 1 (PD-1), inducible T-cell costimulator, CD10, and B-cell lymphoma 6 protein (BCL-6) currently represent the most useful and robust immunohistochemical markers of T_{FH} cells.[3]

A skin manifestation is present in nearly half of all cases,[4,5] and most of these patients present with a nonspecific rash mimicking a drug eruption or viral exanthem.[6,7] However, there are no definitive criteria for diagnosing cutaneous AITL.

Epstein-Barr virus (EBV) is associated with the pathogenesis of several different types of lymphomas, such as natural killer/T-cell lymphoma. EBV-infected B cells are present in 58%-97% of all AITL cases, and in some patients with AITL, EBV-positive B-cell lymphoma secondarily develops.[6,8-11] EBV positivity in nodal tumors has no significant effect on the clinical outcome of patients with AITL.[12,13] However, a study demonstrated that the circulating EBV DNA level is an important prognostic and monitoring marker in patients with AITL.[14]

Although the extent of EBV expression in cutaneous AITL has been reported to range in <1%-50% of the cutaneous infiltrate,[15] effects of EBV positivity on clinicopathologic features are unknown. In the present study, we evaluated the clinical and histopathologic features of cutaneous AITL and analyzed the rate of EBV positivity in skin tumor tissue and its effects on clinicopathologic features.

CAPSULE SUMMARY

- In situ hybridizations are positive for Epstein-Barr virus (EBV) in 19 of 42 (45.2%) patients with cutaneous angioimmunoblastic T-cell lymphoma.
- EBV-positive cutaneous angioimmunoblastic T-cell lymphoma is associated with distinct clinicopathologic features but there is no difference in survival between EBV-positive and EBV-negative cutaneous angioimmunoblastic T-cell lymphoma patients.

METHODS

We searched the Asan Medical Center database for cases diagnosed pathologically as AITL during January 1998-June 2017. Cutaneous AITL was defined as cases with skin involvement diagnosed by using biopsy secondary to systemic AITL. Skin lesions with another etiology, such as fungal infection, viral infection, drug eruption, or eruptions that occurred during a long period of complete remission, were excluded. For example, a case of histologic features of perivascular lymphocytic and eosinophilic infiltration with basal apoptotic bodies and a drug history, which had resolved just after discontinuing a drug, was not considered a skin manifestation of AITL. Immunohistochemical studies with T_{FH} markers (eg, CD10, PD-1, and BCL-6) and T-cell receptor gamma gene rearrangement were used to diagnose cutaneous AITL, especially for cases in which perivascular lymphocytic infiltrates were seen in the absence of atypical lymphocytes. Patients with cutaneous AITL were classified according to EBV in situ hybridization status of skin.

Clinical data were collected from patient medical records at the time of diagnosis. Because of the retrospective design, EBV status was evaluated by EBV in situ hybridization of the tumor. Results of EBV PCR of bone marrow or serum were not evaluated because these data were not available for many of the patients. Overall survival (OS) was calculated from the date of the initial diagnosis to the date of death from any cause or the last follow-up examination. Progression-free survival was calculated from the date of the initial diagnosis to the first day of disease progression, relapse, or last follow-up.

The following features of cutaneous involvement were investigated in patients with cutaneous AITL: skin morphology, site, mean interval from time of initial diagnosis to skin involvement, histopathologic patterns, and immunohistochemical results. Histology was evaluated according to the following 4 patterns: (1) perivascular lymphocytic infiltration without atypical lymphocytes or (2) with atypical lymphocytes, (3) dense, superficial and deep infiltrates of pleomorphic atypical lymphocytes, and (4) vasculitis without atypical lymphocytes.[6]

Statistical analysis

Statistical analyses were performed by using SPSS software version 18.0 (SPSS Inc, Chicago, IL). Comparisons between subgroups of patients were performed by using Student *t* test, the chi-square test, or Fisher's exact test. A survival analysis was performed by using the Kaplan-Meier method, and significance was tested by using the log-rank test. Prognostic factors at the time of diagnosis independently associated with OS were identified by multivariate analysis by using the Cox

proportional hazards regression model. A P value $<.05$ was considered statistically significant.

RESULTS

Clinical findings according to the presence or absence of skin manifestations

A total of 86 AITL cases were identified through a retrospective review of the medical database at Asan Medical Center. Demographic data and clinical features of the patients are summarized in Table I. Of the 86 patients with AITL, 42 (48.8%) showed skin involvement (cutaneous AITL). When clinicopathologic features were compared according to the presence of skin involvement (Table II), B symptoms ($P < .001$) and elevated serum lactate dehydrogenase (LDH) ($P = .005$) were more common in patients with skin involvement than those without. Other clinical variables, such as visceral involvement other than skin and Ann Arbor stage, were not different according to the presence of skin involvement.

Clinicopathologic features of cutaneous AITL

The demographic data and characteristics of the 42 patients with cutaneous AITL are summarized in Table III. At presentation, most patients with skin involvement (24/42, 57.1%) had a nonspecific rash (Fig 1, *A*), followed by papular (10/42, 23.8%; Fig 1, *D*), erythrodermic (7/42, 16.7%; Fig 1, *G*), nodular lesions (4/42, 9.5%; Fig 1, *J* and *M*) and petechial or purpuric patches (3/42, 7.1%; Fig 1, *P*). The histopathologic findings of the 42 patients are summarized in Table III. Most (35/42, 83.3%) cases showed perivascular lymphocytic infiltration of variable depth. Periappendageal infiltration with lymphoid cells was noted in 12 of 42 (28.6%) patients. Seventeen cases had atypical lymphocytic infiltration, and 8 cases had features of mixed inflammation. Twenty cases were classified as perivascular lymphocytic infiltration without atypical lymphocytes (Fig 1, *B* and *H*), 12 as perivascular lymphocytic infiltration with atypical lymphocytes (Fig 1, *E*), 5 with dense, superficial and deep infiltrates of pleomorphic atypical lymphocytes (Fig 1, *K* and *N*), and 5 as vasculitis without atypical lymphocytes (Fig 1, *Q*). Of the 14 cases presenting with papulonodular lesions, 11 (78.6%) cases showed atypical lymphocytes. Atypical lymphocytes were more commonly found in these lesions than lesions of other morphologies, such as nonspecific rash and purpuric patches (3/28, 10.7%; $P < .001$).

The immunohistochemical analysis is summarized in Table III. T_{FH} markers were commonly expressed. CD10 was positive in 30 of 42 (71.4%) patients. PD-1 and BCL-6 were positive in 35 (83.3%) and 28 (66.7%) of the 42 patients, respectively.

Table I. Clinical features of 86 patients with angioimmunoblastic T-cell lymphoma

Characteristic	Value
Sex	
Male	49/86 (57.0)
Female	37/86 (43.0)
Age, y	
Range	28-85
Mean	59.2
Clinical or laboratory feature	
B symptoms	56/86 (65.1)
Hepatosplenomegaly	35/86 (40.7)
Elevated lactate dehydrogenase	72/86 (83.7)
Hypergammaglobulinemia	34/86 (39.5)
Proteinuria	20/86 (23.3)
Elevated β2-microglobulin	54/86 (62.8)
Visceral involvement	31/86 (36.0)
Bone marrow involvement	47/86 (54.7)
Positive Epstein-Barr virus in situ hybridization in lymph node	69/86 (80.2)
Ann Arbor stage	
1	2/86 (2.3)
2	4/86 (4.6)
3	25/86 (29.1)
4	55/86 (63.9)

Values given are N (%), except where indicated.

Clinicopathologic features of cutaneous AITL according to EBV status, EBV positivity, and cutaneous AITL

EBV in situ hybridization positivity in tumor lesions was found in 69 of 86 (80.2%) patients. The frequency of EBV positivity in tumor tissue was significantly higher in patients with skin involvement than in patients without skin involvement ($P = .020$; Table II). EBV in situ hybridization positivity in skin tissue was noted in 19 of 42 (45.2%) patients with cutaneous AITL (Fig 1, *F*, *L*, and *O*). A high percentage of CD79a-positive B cells were EBV in situ hybridization−positive (Fig 1, *F*, *L*, and *O* inset). All patients with EBV-positive skin lesions were also positive for EBV in in situ hybridization of the primary tumor site. Nineteen of 23 patients with EBV-negative cutaneous AITL were positive for EBV in nodal tissue. The clinicopathologic features of cutaneous AITL according to EBV status of skin lesions are summarized in Tables II and III. Skin lesion EBV positivity was higher in patients with papular or nodular lesions than those with nonspecific rash or purpuric patches ($P < .001$). The other clinical features (eg, B symptoms, serum LDH level, and Ann Arbor stage) were not dependent on EBV positivity of skin lesions among patients with cutaneous AITL (Table II). A pattern of dense, superficial and deep infiltrates of

Table II. Comparison of patient demographics and clinical features of AITL according to skin involvement

Characteristic	Cutaneous AITL, N = 42			AITL without skin involvement, N = 44*	*P* value†	*P* value‡
	EBV positive, n = 19*	EBV negative, n = 23*	*P* value			
Sex			.801		.685	.634
Male	10/19 (52.6)	13/23 (56.6)		26/44 (59.1)		
Female	9/19 (47.3)	10/23 (43.5)		18/44 (40.9)		
Age, y					.371	**.047**
≥60	38-85	28-85		31-82		
Mean	63.2	60.2		56.4		
Clinical or laboratory feature						
B symptoms	17/19 (89.5)	19/23 (82.6)	.522	19/44 (43.2)	**<.001**	**.001**
Hepatosplenomegaly	10/19 (52.6)	9/23 (39.1)	.382	16/44 (36.4)	.402	.229
Elevated LDH	19/19 (100)	21/23 (91.3)	.492	32/44 (72.7)	**.005**	**.011**
Hypergammaglobulinemia	9/19 (47.3)	9/23 (39.1)	.591	16/44 (36.4)	.538	.413
Proteinuria	5/19 (26.3)	5/23 (21.7)	.729	10/44 (22.7)	.905	.759
Elevated β2-microglobulin	12/19 (63.2)	13/23 (56.6)	.663	29/44 (65.9)	.540	.833
Visceral involvement	11/19 (57.9)	7/23 (30.4)	.073	13/44 (29.5)	.199	**.033**
Bone marrow involvement	13/19 (68.4)	10/23 (43.5)	.106	24/44 (54.5)	.984	.305
Positive EBV in situ hybridization in lymph node	19/19 (100)	19/23 (82.6)	.114	31/44 (70.4)	**.020**	**.006**
Ann Arbor stage			.163		.063	**.025**
1	0/19 (0)	0/23 (0)		2/44 (4.5)		
2	0/19 (0)	1/23 (4.3)		3/44 (6.8)		
3	3/19 (15.8)	7/23 (30.4)		15/44 (34.1)		
4	16/19 (84.2)	15/23 (65.2)		24/44 (54.5)		

P values <.05 (bolded) were considered statistically significant.
AITL, Angioimmunoblastic T-cell lymphoma; *EBV*, Epstein-Barr virus; *LDH*, lactate dehydrogenase.
*Values are n (%) except where indicated.
†Compared between patients with and without skin involvement.
‡Compared between patients with EBV-positive skin involvement and patients without skin involvement.

pleomorphic atypical lymphocytes was more common in cases with EBV-positive cutaneous AITL (P = .014; Fig 1, *L* and *O*; Table III). EBV-negative cutaneous AITL was more commonly associated with perivascular lymphocytic infiltration without atypia (P < .001; Fig 1, *C, I*, and *R*). Lymphocyte atypia was significantly more common in EBV-positive skin lesions (P = .006; Fig 1, *F, L*, and *O*; Table III).

When clinical features of patients with EBV-positive cutaneous AITL were compared with those without skin involvement (Table II), the frequencies of Ann Arbor stage 4 (P = .025), elevated serum LDH level (P = .011), visceral involvement (P = .033), and B symptoms (P = .001) were significantly higher in patients with EBV-positive skin involvement. Patients with EBV skin involvement were significantly older than those without skin involvement (P = .047).

Survival outcome

The follow-up period ranged 1-141 (median 61) months. When all 86 patients were combined into a single cohort, the 5-year survival rate was 32.2%. When survival outcomes were evaluated by the presence of skin involvement, the presence of skin lesions did not affect survival outcome (Fig 2, *A*; P = .554). EBV positivity of nodal tissue also did not affect survival (Fig 2, *B*; P = .378). The median OS of the 42 patients with cutaneous AITL was 27.0 months. OS in patients with EBV-positive cutaneous AITL was not significantly different than that of patients with EBV-negative cutaneous AITL (Fig 2, *C*; P = .183). When survival was compared between patients with and without skin involvement, OS (P = .035, Fig 2, *D*) and progression-free survival (P = .042) of patients with EBV-positive cutaneous AITL was significantly worse.

In a univariate analysis, age >60 years, advanced Ann Arbor stage, EBV-positive skin involvement (hazard ratio 1.69, 95% confidence interval 1.13-4.65; P = .037), elevated serum LDH, and B symptoms were associated with a worse OS in AITL. The multivariate analysis revealed that age >60 years, advanced Ann Arbor stage, and EBV-positive skin involvement (hazard ratio 1.42, 95% confidence interval 1.07-5.06; P = .044) were independent prognostic markers for a worse OS.

Table III. Clinicopathologic features of cutaneous AITL

Clinicopathologic feature	All cutaneous AITL, N = 42, n (%)	EBV-positive cutaneous AITL, N = 19, n (%)	EBV-negative cutaneous AITL, N = 23, n (%)	*P* value
Cutaneous				
Morphology				
Nonspecific rash	24/42 (57.1)	7/19 (36.8)	17/23 (73.9)	**.016**
Erythrodermic	7/42 (16.7)	2/19 (10.5)	5/23 (21.7)	.428
Papulonodular	14/42 (33.3)	12/19 (63.2)	2/23 (8.7)	**<.001**
Petechial or purpuric patch	3/42 (7.1)	0/19 (0)	3/23 (13.0)	.667
Mean interval to skin manifestation, mon, range	7.4 (0-14.8)	7.1 (0-12.3)	7.6 (0-15.2)	.647
Histopathologic				
Atypical lymphocytes	17/42 (40.5)	13/19 (68.4)	6/23 (26.1)	**.006**
Mixed inflammatory infiltrates	8/42 (19.0)	2/19 (10.5)	6/23 (26.1)	.258
Perivascular lymphocytic infiltration	35/42 (83.3)	14/19 (73.7)	21/23 (91.3)	.214
Periappendageal lymphocytic infiltration	12/42 (28.6)	5/19 (26.3)	7/23 (30.4)	.769
Epidermotropism of lymphocytic infiltration	0/42 (0)	0/19 (0)	0/23 (0)	1
Panniculitis-like infiltration	0/42 (0)	0/19 (0)	0/23 (0)	1
Pattern of lymphoid infiltrates				
Perivascular lymphocytic infiltration without atypical lymphocytes	20/42 (47.6)	3/19 (15.8)	17/23 (73.9)	**<.001**
Perivascular lymphocytic infiltration with atypical lymphocytes	12/42 (28.6)	8/19 (42.1)	4/23 (17.4)	.098
Dense, superficial and deep infiltrates of pleomorphic atypical lymphocytes	5/42 (11.9)	5/19 (26.3)	0/23 (0)	**.014**
Vasculitis without atypical lymphocytes	5/42 (11.9)	3/19 (15.8)	2/23 (8.7)	.644
Immunophenotype				
CD4	38/42 (90.5)	17/19 (89.5)	21/23 (91.3)	1
CD8	27/42 (64.3)	12/19 (63.2)	15/23 (65.2)	.890
CD20	13/42 (31.0)	6/19 (31.6)	7/23 (30.4)	.936
CD10	30/42 (71.4)	14/19 (73.7)	16/23 (69.6)	.769
Programmed cell death 1	35/42 (83.3)	15/19 (78.9)	20/23 (87.0)	.682
B-cell lymphoma 6	28/42 (66.7)	14/19 (73.7)	14/23 (60.9)	.381
T-cell receptor gamma gene rearrangement				
Monoclonality	12/18 (28.6)	4/7 (57.1)	8/11 (72.7)	.627

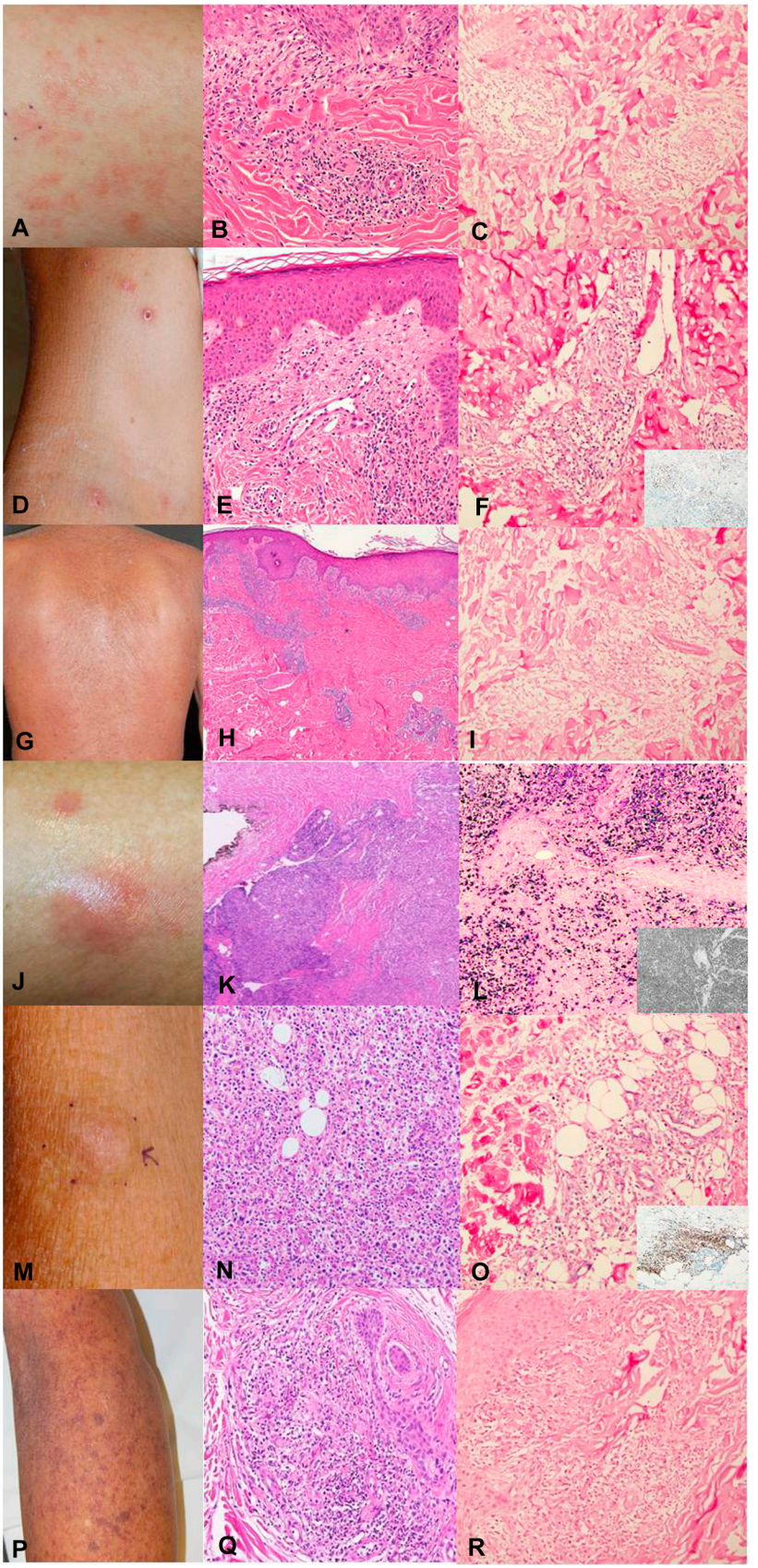
P values <.05 (bolded) were considered statistically significant.
AITL, Angioimmunoblastic T-cell lymphoma; *EBV*, Epstein-Barr virus.

DISCUSSION

Similar to previous reports,[4,16-18] half of patients with AITL had skin manifestations, and the skin manifestation had various cutaneous morphologies, including nonspecific rash, erythroderma, purpuric patches, or papulonodular lesions. We analyzed the association between skin involvement and clinical features with survival of patients with AITL. Although most patients with cutaneous AITL had advanced Ann Arbor stage at the diagnosis of skin involvement, no significant differences in clinical features were observed, except for B symptoms and elevated serum LDH, depending on the presence of skin involvement.

To some extent, the features of cutaneous involvement in our patients corresponded with the 4 patterns described by Martel et al.[7] However, lymphocytic infiltrates exhibited not just a superficial perivascular pattern but were also more deeply perivascular. Furthermore, in some cases, lymphocytic infiltrates had perivascular and periappendageal patterns. In a previous report, about half of skin biopsies revealed mixed inflammation, demonstrated by lymphohistiocytic infiltrations with plasma cells or eosinophils.[19] In the present study, mixed inflammatory infiltration was observed in only 8 of 42 skin biopsies. Furthermore, we revealed that papulonodular lesions mainly consisted of atypical lymphocytes distributed in superficial or deep dermis with a perivascular or periappendageal pattern.

We evaluated the clinicopathologic features of cutaneous AITL according to EBV positivity in skin lesions. To the best of our knowledge, the present study is currently the largest study to evaluate the clinicopathologic features of cutaneous AITL and the significance of EBV positivity in skin lesions. Although the prognostic significance of serum EBV DNA copy number and nodal EBV positivity has been evaluated,[13,14,20] the significance of EBV positivity in skin lesions has not been examined.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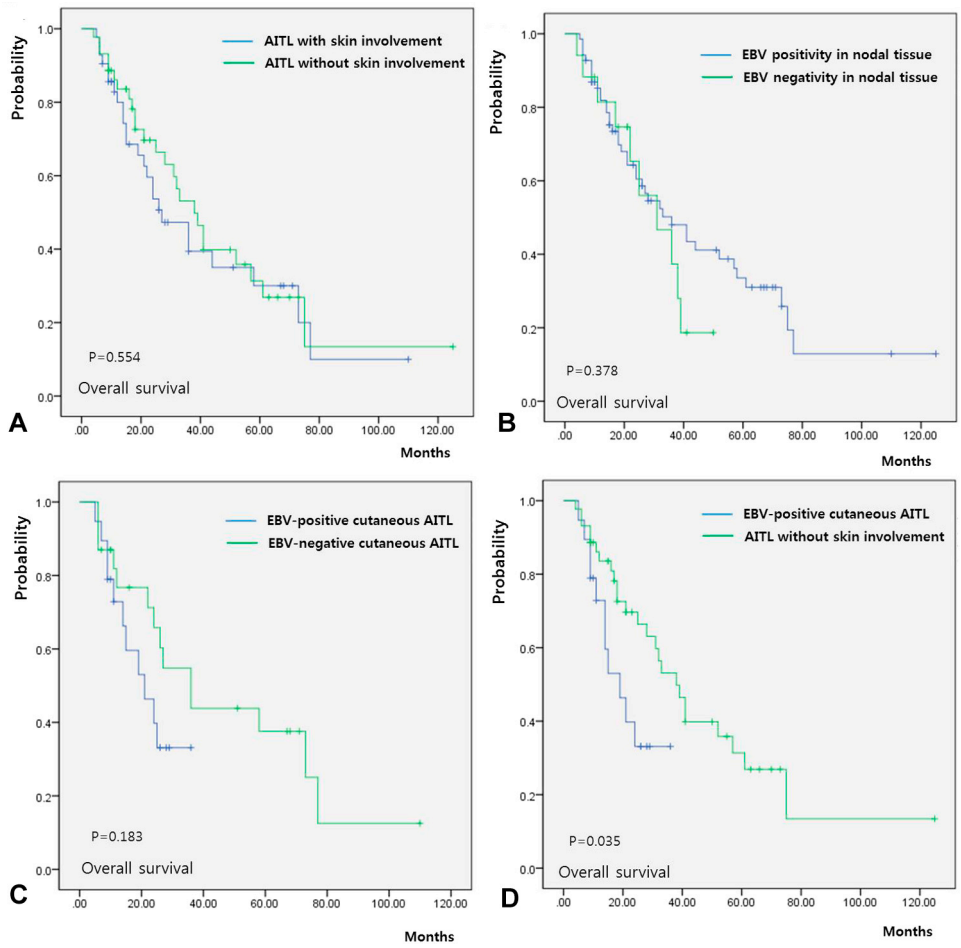

Fig 2. Comparison of survival by AITL clinical variable. **A**, Difference in overall survival (OS) depending on skin involvement. **B**, Difference in OS depending on EBV positivity in nodal tissue. **C**, Difference in OS depending on EBV positivity in skin tissue from patients with cutaneous AITL. **D**, Difference in OS between patients with EBV-positive cutaneous AITL and patients without skin involvement. *AITL*, Angioimmunoblastic T-cell lymphoma; *EBV*, Epstein-Barr virus.

Fig 1. Clinicopathologic features and Epstein-Barr virus (EBV) positivity of cutaneous angioimmunoblastic T-cell lymphoma (AITL). **A**-**C**, Patient 1. **A**, Multiple erythematous macules on abdomen. **B**, Perivascular lymphocytic infiltration without atypia. **C**, Negative EBV in situ hybridization in skin tissue. **D**-**F**, Patient 2. **D**, Multiple erythematous excoriated papules on upper arm. **E**, Perivascular lymphocytic infiltration with small-to-medium−sized pleomorphic atypical lymphocytes. **F**, Scattered EBV-positive lymphoid cells. **Inset**, immunohistochemical study with CD79a. **G**-**I**, Patient 3. **G**, Fine-scale erythroderma on whole body. **H**, Perivascular lymphocytic infiltration without atypia. **I**, Negative EBV in situ hybridization in skin tissue. **J**-**L**, Patient 4. **J**, Multiple erythematous subcutaneous nodules on leg. **K**, Dense, superficial and deep infiltrates of pleomorphic atypical lymphocytes from skin lesion presenting a solitary nodule. **L**, Positive EBV in situ hybridization in skin tissue. **Inset**, immunohistochemical study with CD79a. **M**-**O**, Patient 5. **M**, A solitary well-demarcated flesh-colored nodule on forearm. **N**, Diffuse nodular infiltration of pleomorphic atypical lymphocytes. **O**, Positive EBV in situ hybridization in skin tissue. **Inset**, immunohistochemical study with CD79a. **P**-**R**, Patient 6. **P**, Multiple erythematous-to-purpuric macules and patches on forearm. **Q**, Vasculitis without atypical lymphocytes. **R**, Negative EBV in situ hybridization in skin tissue. (**B**, **E**, **H**, **K**, **N**, and **Q**, Hematoxylin-eosin stain; original magnifications: **B** and **E**, ×100; **H** and **K**, ×40; **N** and **Q**, ×200; **C**, **F**, **F inset**, **I**, **L**, **L inset**, **O**, **R**, in situ hybridization; original magnification: ×100.)

EBV is a ubiquitous herpes virus that infects >90% of all humans and is classified as a group 1 human carcinogen by the International Agency for Research on Cancer because of the etiologic role it plays in lymphomas, such as Hodgkin lymphoma, natural killer/T-cell lymphoma, and AITL.[21] EBV modulates the production of cytokines, which might promote the acquisition of tumor-promoting inflammatory conditions.[22,23] In Hodgkin lymphoma, latent EBV infection modifies the functioning of tumor-infiltrating inflammatory cells, which interact with Reed-Sternberg cells.[24-27] The presence of EBV in tumor cells of patients with Hodgkin lymphoma has prognostic significance in survival outcomes.[28-31]

Histologic progression in AITL according to EBV positivity has been reported.[32,33] Attygalle et al reported the histologic evolution of nodal AITL during disease progression.[32] Initial lesions with subtle histologic findings can progress to typical AITL lesions with more numerous and diffusely distributed neoplastic T cells.[32] EBV positivity is higher in more mature lesions and occasionally form diffuse sheet patterns.[33] A role for EBV in the clinicopathologic presentation and outcome of AITL has been suggested. Battegay et al reported a case of AITL with complete remission after treatment with antiviral agents.[34] They demonstrated that enlarged LNs and systemic symptoms are correlated with the serum EBV load.[34]

In the present study, a significant difference in the morphology of skin lesions depending on EBV positivity on skin tissue was seen. It is unclear whether there are changes in cutaneous morphology during disease progression because we did not perform consecutive biopsies. However, similar to the histologic evolution in nodal lesions, cutaneous AITL could have a histopathologic spectrum during disease progression. Skin lesions presenting histologically as papulonodules composed of dense infiltrates of tumor cells were associated with a higher frequency of EBV positivity.

The prognosis for AITL is poor, with most studies reporting a median survival of <3 years, even when treated intensively.[8,16,17,35,36] Various results have been reported on the effect of skin involvement in survival of patients with AITL.[5,16,17,35] In the present study, no significant association was found between the presence of skin involvement and survival. Previous studies on the prognostic impact of EBV positivity in patients with AITL have yielded varying results. The presence of circulating EBV DNA is strongly associated with the presence of circulating AITL tumor cells.[37] Circulating EBV DNA level is an important prognostic and monitoring marker for AITL.[14] However, EBV DNA copy number in tumor tissues does not correlate with survival,[20] and EBV in situ hybridization of LN biopsies has no effect on the prognosis of AITL.[13] The prognostic value of EBV positivity in skin lesions of AITL has not been evaluated.

Although EBV positivity in skin lesions is not a prognostic index among patients with cutaneous AITL, it has prognostic value when evaluated between patients without skin involvement and patients with EBV-positive cutaneous AITL. EBV positivity in skin lesions was an independent prognostic factor in AITL. In contrast with skin tissue, EBV positivity in nodal tissue was not a prognostic index, which might be related to the high positivity rate of >80% in nodal tissue. The prognostic value of EBV positivity in skin tissue suggests a tumor-promoting function for EBV. Tumor-promoting functions of EBV in hematologic malignancies have been suggested.[22-25] Because a previous study suggested a tumor-promoting function for circulating EBV DNA in AITL,[14,37] EBV positivity in skin tissue could be related to circulating EBV copy number. Patients with EBV-positive cutaneous AITL were older than patients without skin involvement in the present study. Immunosenescence in elderly patients is associated with decreased T-cell function and might increase the number of latently EBV-infected B cells, resulting in an increased risk of developing EBV-positive cutaneous AITL.[38,39]

The limitations of the present study are the retrospective design and loss of data, such as serum EBV DNA copy number. In a previous study, the detection of EBV in peripheral blood mononuclear cells was correlated with EBV positivity in LN biopsies, but the correlation between serum EBV DNA level and EBV positivity in skin lesions was unclear.[37] It was difficult to assess the entire spectrum of clinical manifestations in this retrospective study design.

In conclusion, EBV positivity in skin lesions is associated with peculiar clinicopathologic features in patients with cutaneous AITL. EBV positivity in skin tissue predicts worse prognosis in patients with AITL.

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