Angiocentric T cell Lymphoma associated with Epstein-Barr Virus

Ji-Yong Park, M.D., Nack-In Kim, M.D.

Department of Dermatology, College of Medicine, Kyung Hee University, Seoul, Korea

Angiocentric T-cell lymphomas have been described as a distinctive clinicopathologic entity in the spectrum of peripheral T-cell lymphomas, with a prominent invasion of blood vessels by lymphomatous cells. In these conditions, the presence of Epstein-Barr virus (EBV) genomes has been demonstrated, suggesting that EBV might play a major role in their cause.

Herein, we report a case of cutaneous angiocentric T cell lymphoma associated with the EBV. The patient was diagnosed with nasal angiocentric T cell lymphoma 5 months ago, and treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) combination chemotherapy. After three cycles of CHOP, skin lesions developed. A skin biopsy specimen showed an angiocentric and angioinvasive infiltrate containing some atypical lymphocytes. EBV encoded RNA (EBER) was demonstrated in lesional skin by in situ hybridization.

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Key Words : Angiocentric T cell lymphoma, EBV

Angiocentric T-cell lymphoma is at the malignant end of a histological spectrum of angiodestructive disorders termed angiocentric immunoproliferative lesions(AIL). AIL is made up of extranodal malignant lymphomas of B-cell, T-cell or NK-cell origin1. It is considered to progress histologically from the polymorphous to the monomorphous stage. EBV has been implicated in the pathogenesis of the AIL group[2-5], and it has been suggested that it mediates the common histological features of the vascular lesions.

Herein, we report a patient with EBV associated angiocentric T cell lymphoma.

CASE REPORT

A 44-year-old man was presented with multiple erythematous nodules on his arm and both legs. In December 1997, he had had a nasal obstruction. He had been diagnosed as sinusitis at the otorhinolaryngology department. These symptoms had fluctuated and progressed for three months. At that time, the biopsy specimen from the nasal cavity had been taken and interpreted as nasal angiocentric T cell lymphoma. He had been treated with a CHOP(cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen for 5 months. In July 1998, the skin lesions developed and he was referred to our department for the evaluation of the skin lesions. The lesions were multiple, tender, variable sized reddish colored and had a firm consistency located on the upper and lower extremities (Fig. 1). Family history and his medical history were not contributory. There was no constitutional symptoms such as fever, night sweats or weight loss. A physical examination revealed no abnormalities such as cervical lymphadenopathy or hepatosplenomegaly. Laboratory findings of the following studies were either negative or normal : complete blood cell count, liver function test, urinalysis, chest X-ray, abdominal computed tomography and bone marrow biopsy. A skin biopsy specimen obtained from the right arm showed a scanty, perivascular infiltration of lym-

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Reprint request to : Ji-Yong Park, M.D., Department of Dermatology, College of Medicine, Kyung Hee University, Seoul, Korea

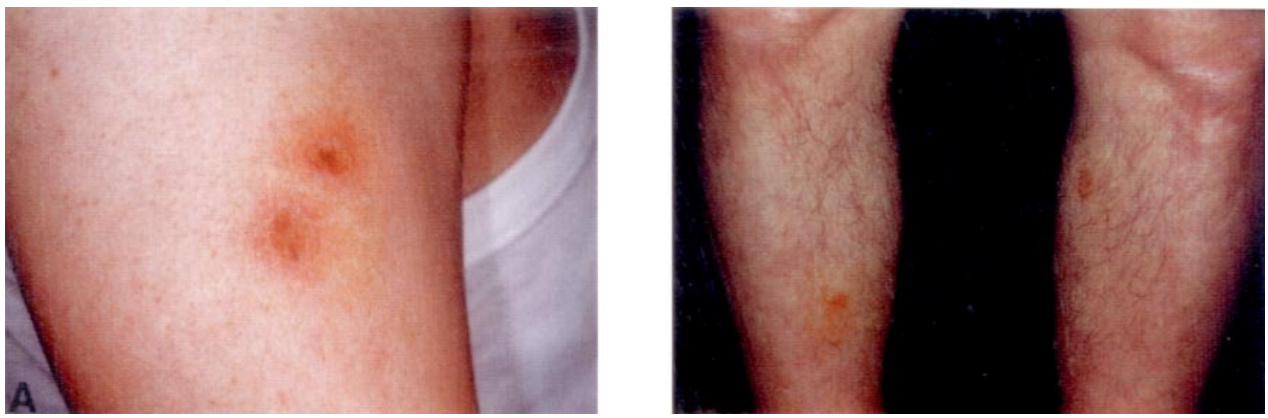

Fig. 1. A tender 1.5×1.5 cm-sized firm erythematous nodule with central necrotic crust on the right arm(A), Scattered tender erythemaous patch and nodule on both legs(B).

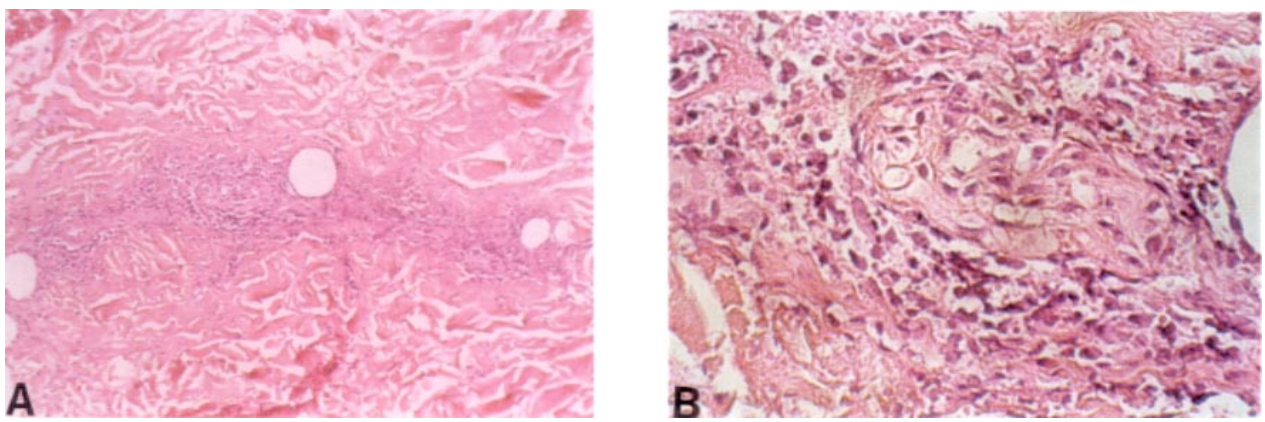

Fig. 2. (A) A photomicrograph revealed the infiltration of mononuclear cells and focal necrosis around the vessels in deep dermis(H&E X100). (B) High magnification showed a atypical polymorphic angiocentric lymphohistiocytic infiltration and angiodestruction(H&E ×200).

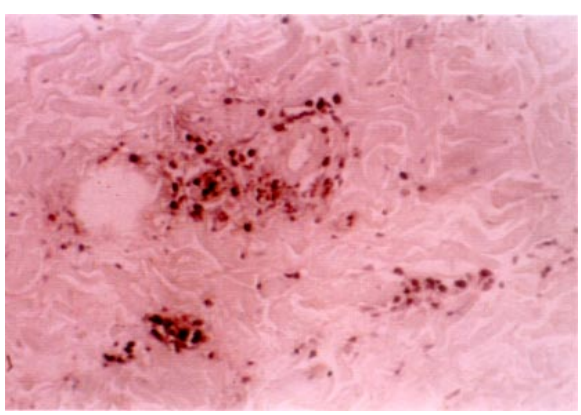

Fig. 3. Nuclear positivity for EBV genome in infiltrative tumor cells (in situ hybridization ×100).

phoid cells and focal necrosis in the dermis (Fig. 2). The involved vessels were surrounded by polymorphic, atypical lymphoid cells with hyperchromatic nuclei. The immunohistochemical studies revealed that most of the infiltrated lymphocytes were positively stained for CD3, CD45RO (UCHL-1) and LCA (leukocyte common antigen) whereas CD20, CD30 (Ki-1), CD56, and CD57 showed no immunoreactivity. EBV-encoded small nuclear RNA (EBER) was detected in lesional tissue by the in situ hybridization. EBER positive cells were observed around dermal blood vessels corresponding to lymphoid cells in lesional H&E tissue sections (Fig.3). After the skin lesions were diagnosed as cutaneous angiocentric T cell lymphoma, he was recommended to be treated

Table 1. Reported cases of angiocentric T-cell lymphoma in Korean dermatologic literature

No.	Age/Sex	Location	Skin lesion	Extracutaneous involvement	EBER	Therapy	Reference
1	34/M	Thigh	Patches, plaques	Splenomegaly, testis, maxillary sinus	+	COPBLAM, RT	8
2	47/M	Whole body	Patches, plaques	Hepatomegaly	+	AMA	8
3	64/F	Upper limbs	Deep nodules	Splenomegaly	+	CHOP	8
4	43/M	Trunk, arms	Ulcerative plaques	Splenomegaly, LN	+	BACOP	8
5	43/F	Back, limbs	Deep nodules	None	-	CHOP	8
6	34/F	Lower limbs	Deep nodules	LN, tonsil	+	COPBLAM	8
7	41/M	Trunk, genitalia	Necrotic papules, nodules	Splenomegaly, LN, BM, kidney, GI	-	BVP	8
8	49/F	Abdomen	Ulcerative papules	None	+	COPBLAM-V	8
9	61/M	Whole body	Deep nodules, splaque	None	+	Cs + Pd	8
10	32/M	Abdomen	Plaques	Lung	+	CHOP	8
11	62/F	Flank	Plaques	None	+	Cs + Pd	8
12	41/F	External genitalia	Ulcer	Nose, eye, uterine cervix	not done	Promace-Cytabom	8
13	61/M	Whole body	Nodules, plaques	none	+	Cs + Pd	9
14	42/F	Whole body	Plaques	none	+	Cs + Pd	9
15	32/M	Abdomen	Ulcer, plaque	none	+	Cs + Pd	9
16	60/M	Back	Plaques	none	-	Cs + Pd	9
17	82/F	Trunk, upper limbs	Necrotic nodules	nose	+	CVP	10
18	35/F	Face	Necrotic nodules	none	+	CHOP	11
*	44/M	Upper, lower limbs	Nodules	nose	+	CHOP	our case

RT: radiation therapy, LN: lymph node enlargement, GI: gastrointestinal tract,
BM: bone marrow
Chemotherapeutic regimens
C or Cs = cyclophosphamide, H or A = adriamycin, O or V = oncorvin(or vincristine)
P or PD = prednisolone, B or BL = Bleomycin, M = methotrexate
Promace-Cytabom = cytoxan + adriamycin + etoposide + prednisolone

with other chemotherapeutic agents. But he refused further chemotherapy.

DISCUSSION

Angiocentric T cell lymphoma(ACL) have been described as the malignant form of angiodestructive disorders termed angiocentric immunoproliferative lesions(AIL). The conception of AIL was first proposed by Jaffe[6]. The spectrum includes benign lymphocytic vasculitis, lymphomatoid granulomatosis/polymorphic reticulosis, and angiocentric lymphoma; and the diseases show a prominent vascular invasion and predominant occurrence in extranodal sites. ACL has been reported with significant frequency in Asia[7].

To our knowledge, 18 cases of ACL have been reported in Korean dermatologic literature[8-11]. These patients were relatively young, with an average age of 42 years(range, 32 to 82 years). The cutaneous lesions were nodules or plaques, and were ulcerated or had intact skin. Ten patients had evidence of extracutaneous involvement. All patients were treated with combination chemotherapy(Table 1).

Clinically, ACL is commonly present along the midline of the face, especially the nasal region which is the most common site of presentation. Additionally skin, soft tissue, testis, upper respiratory tract and gastrointestinal lesions have been reported. The skin and subcutaneous tissue are the most common sites of secondary spread[7,12]. In our case, the nasal lesion was the first and the cutaneous lesions

were thought to be the secondary spread from the nasal lesions.

The major histological features of ACL of the skin are a perivascular and periadnexal infiltration of lymphoma cells in the mid to deep dermis, with frequent involvement of the subcutaneous layer[13]. A prominent feature of ACL is lymphomatous infiltration of small, medium sized or large blood vessels. A workshop[7] of ACL in the nose and other extranodal sites proposed that nasal T/NK cell lymphoma is a distinct clinicopathological entity highly associated with EBV, which has a characteristic immunophenotype: CD2 positive and CD56 positive, but usually negative for surface CD3. Cytoplasmic CD3 can be detected in the paraffin section. The surface marker for B cells were negative and immunoglobulin gene rearrangement was not detected. In addition, tumours were recognized in other extranodal sites, and the provisional term 'nasal type' T/NK cell lymphoma was recommended. EBV has been implicated in the pathogenesis of AIL group[2-5], and it has been suggested that it mediates the common histological features of the vascular lesions. Because virtually all cases of nasal T/NK cell lymphoma are positive for EBV, in situ hybridization studies with probes to EBER may be very helpful in the diagnosis and can detect even small numbers of neoplastic cells. In our case, although the number of neoplastic cells was small, the presence of EBER positive cell could help to diagnosis the cutaneous lesions.

The differential diagnosis includes lymphomatoid granulomatosis, malignant angioendotheliomatosis and subcutaneous T cell lymphoma. Lymphomatoid granulomatosis exhibits many similarities to ACL and was only recently considered part of the same disease spectrum. However, recent data indicates that, in the majority of cases, lymphomatoid granulomatosis is a B-cell proliferation, associated with an exuberant T-cell reaction[18]. Malignant angioendotheliomatosis is characterized by the predominantly intravascular location of the lymphoma cells, as opposed to the predominantly extravascular and intramural location in ACL. Most cases have B-cell phenotype[19,20]. Histologically, the distinction between ACL involving skin and T cell lymphoma commonly involving subcutaneous tissue is difficult. Because the subcutaneous tissue is often involved in both lesions[13,21]. Although ACL commonly involves multiple organ systems in addition to the skin, some cases of ACL are present only with a cutaneous disease. Moreover, both ACL and subcutaneous T cell lymphoma have been reported with fatal outcomes and hemophagocytic syndrome[13,16,22,23]. However, ACL commonly involved vessel and necrosis would be extensive in association with a latent EBV.

Multiagent chemotherapy for treatment is recommended, but the clinical course is usually aggressive and refractory to chemotherapy. Definite prognostic factors have not been determined. Some authors consider that strong EBER expression is an important indicator of poor prognosis[14,15]. A hemophagocytic syndrome is a common clinical complication, which adversely affects survival in ACL[13,16]. But our patient did not develop the syndrome at presentation, with normal complete blood cell count, coagulation studies and bone marrow biopsy. This syndrome can occur at any time during the clinical course and usually pursues a rapidly fatal clinical course over a period of several weeks. The mechanism of lymphoma associated hemophagocytic syndrome is unknown. Simrell et al[17]. identified a phagocytosis-inducing factors from ACL. In some cases, lymphoma and infection may act as cofactors during reactive hemophagocytosis.

We report herein a case of ACL associated with EBV which was different to other T-cell lymphoma of the skin because of its histological, immunohistological features and association with EBV.

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