Two Cases of the Angioimmunoblastic Lymphadenopathy Type of Peripheral T-cell Lymphoma : Different Clinical Courses According to Positivity to Epstein-Barr Virus

Jae Wang Kim, M.D., Sang Ho Nam, M.D., Kwang Joong Kim, M.D., Chong Min Kim, M.D., Chong Ju Lee, M.D.

Department of Dermatology, College of Medicine, Hallym University, Seoul, Korea

Peripheral T-cell lymphoma(PTCL) encompasses histopathologically and clinically various spectra of cutaneous T-cell lymphoma(CTCL). In this report, we describe two cases of PTCL showing different clinical courses according to EBV(Epstein-Barr virus) positivity. The clinical course of case 1 with EBV-associated PTCL was rapidly fatal and refractory to intensive chemotherapy. However, in case 2, EBV genomes were not found in her lesional tissues and she showed an indolent clinical course without systemic symptoms. Accordingly, serological and immunohistochemical investigations for EBV might be mandatory in cutaneous PTCL to evaluate clinical prognosis. (Ann Dermatol 10:(2) 116~122, 1998)

Key Words : Peripheral T-cell lymphoma, EBV

Besides classical CTCL such as mycosis fungoides/Sézary syndrome, CTCL encompasses clinicopathologically heterogeneous variants such as Ki-1 positive or negative diffuse large T-cell lymphoma, human T-cell lymphotropic lymphoma/leukemia virus-1(HTLV-1) positive adult T-cell lymphoma, angiocentric T-cell lymphoma(ACTCL), subcutaneous T-cell lymphoma, and secondary PTCL[1]. Secondary PTCL, CD56+ PTCL and ACTCL in particular, are characterized by an aggressive clinical course, common extranodal involvement, frequent association with EBV, and the histopathological findings of non-epidermotrophism, angiocentricity and angioinvasion[1-3]. It has been recently shown that PTCL which contains EBV, follows a rapidly fatal course in comparison with EBV-negative counterparts[1-5]. We herein report two cases of PTCL, which showed different clinical features according to

serological and immunohistochemical positivity to EBV.

CASE REPORT

Case 1

A 29-year-old man had had skin lesions on his right flank area and both shins for 1 month. Over the 1 month before his visit, a sustained fever, weight loss and night sweats were experienced. An examination revealed purplish colored, crusted ulcerative plaques on his right flank area and brownish fine scaling patches on his shins(Fig. 1). Both inguinal lymphadenopathies were found. His hemoglobin was 6.2 gm/dl, the leukocyte count, 1,800/mm³, and platelet count, 59,000/mm³. No atypical lymphocytes were found in the peripheral blood. A bone marrow aspiration revealed hypocellular spaces with increased hemophagocytosis. A chest CT scan revealed an inhomogenous nodular density, suggesting malignant lymphoma. An inguinal biopsy showed angioimmunoblastic lymphadenopathy(AILD). Although he received intensive combined chemotherapy with a CVP regi-

Fig. 1. Purplish colored, crusted ulcerative plaques on the right flank area(A) and brownish fine scaling patches on the shins in case 1(B).

Fig. 2. A skin biopsy specimen taken from the abdomen showing a dense admixture of small or large hyperchromatic angulated mononuclear cells infiltrating in the dermis and subcutis(A, H&E, ×100(right), × 400(left)). Multiple histiocytes representing reactive hemophagocytosis syndrome(B, H&E, × 400). The overlying epidermis revealed severe necrotic changes and focal exocytosis in case 1(C, H &E, ×200).

men(cyclophosphamide, vincristine, prednisolone), he disclosed unremittable fever and finally died of sepsis.

Case 2

A 56-year-old woman had multiple skin lesions of

2 years' dutation. She had no fever, weight loss, night sweats and hepatosplenomegaly except for mild inguinal lymphadenopathy. An examination re-

Fig. 3. Positive findings of infiltrative cells to CD45RO(A, ×200) and CD8(B, ×200) in case 1.

Fig. 4. Positive hybridization signals corresponding to EBV DNA genomes in case 1(A, in situ hybridization to EBER-1, ×200). Positive bands at 3-kb in lesional tissue DNA when hybridized with Bam HI-W fragments and at 12-kb when hybridized with Bam HI-A fragments in case 1(B, Southern blot hybridization, lane M: Marmoset cell line(B95.8), lane N: normal control, lane 1: case 1, lane 2: case 2).

vealed erythematous infiltrative nodules with smooth surfaces on her back(Fig. 5). Her hemoglobin was 14.3gm/dl, the leukocyte count, 13,000/mm³, and platelet count, 140,000/mm³. A bone marrow aspiration and peripheral blood smear were negative for neoplastic cells. An abdominal CT scan demonstrated paraaortic lymphadeopathy. An inguinal biopsy showed AILD with widespread proliferation of arborizing small vessels and deposition of amorphous materials in the blood vessel walls(Fig. 6). After 5 cycles of chemotherapy with a CHOP(cyclophosphamide, adriamycin, vincristine and prednisolone) regimen, her skin lesions were attenuated slowly. She is in relatively good health without any systemic symptoms up to the present date.

Morphologic and Immunophenotypic Studies

Skin specimens from both cases were fixed in neutral buffered formalin and processed for Hema-

Fig. 5. Multiple brownish infiltrative papules with smooth surfaces on the back in case 2.

Fig. 6. Inguinal biopsy showing angioimmunoblastic lymphadenopathy in case 2(H & E, ×400).

Fig. 7. A skin biopsy specimen demonstrating angiocentricity and angiodestruction by atypical lymphoid cells were also found in case 2(A, H & E, ×400). Immunophenotypically CD45RO(B, ×200) and CD8(C, ×200) positive lymphoid cells in case 2.

toxylin-Eosin-stained sections. In case 1, a skin biopsy specimen taken from his abdomen showed a dense admixture of small or large hyperchromatic angulated mononuclear cells infiltrating in the dermis and subcutis(Fig. 2-A). The vessels and sweat glands were extensively permeated and distorted by atypical lymphoid cells with fibrinoid deposits. Multiple histiocytes phagocytizing hemopoietic cellular remnants, were found in the lower dermis, representing reactive hemophagocytosis syn-

drome(Fig. 2-B). The overlying epidermis revealed severe necrotic changes, blistering and focal exocytosis without Pautrier's microabscesses(Fig. 2-C). In case 2, a skin biopsy specimen taken from her back demonstrated extensive polymorphous infiltration of small to medium-sized atypical lymphoid cells mainly in skin appendigeal foci and perivascular areas. Angiocentricity and angiodestruction by atypical lymphoid cells were also found(Fig. 7-A). However, the overlying epidermis was relatively intact and hemophagocytotic findings were not observed.

The standard avidin-biotin complex immunoperoxidase method was used to determine the immunophenotypes in paraffin-embedded sections with a wide panel of monoclonal antibodies. In case 1, lymphoid infiltrates reacted with CD45, CD45RO and CD8(Fig. 3-A, B). However, positiveness was not found aganist CD2, CD3, CD4, CD19, CD20, CD30 and CD68. In case 2, CD45, CD45RO and CD8 positive lymphoid cells were found(Fig. 7-B, C). But none of the infiltrative cells expressed CD2, CD3, CD4, CD19, CD20, CD30 and CD68.

Serologic Studies of Antibodies to EBV

Serologic tests of antibodies as IgM/IgG EBV-viral capsid antigen(VCA), IgG early antigen(EA), IgG EBV nuclear antigen(EBNA) were performed. Positiveness of IgM anti-VCA, a titer of IgG anti-VCA higher than 1:640, a titer of IgG anti-EA higher than 1:10, or positivity of IgG anti-EBNA, were regarded as positive datas. In case 1, IgM anti-VCA was negative, the titers of IgG anti-VCA were 1:720, IgG anti-EA was below 1:10, IgG anti-EBNA was positive. In case 2, the titers of antibodies were negative to IgM anti-VCA, 1:50 for IgG anti-VCA, below 1:10 for IgG anti-EA, and negative to IgG anti-EBNA.

DNA Hybridization Studies for EBV

We performed in situ hybridization for EBV nuclear genomes from paraffin-embedded tissues of the skin biopsy with a fluorescein-conjugated oligonucleotide probe(EBER-1, EBV encoded RNA). After the deparaffinized tissue specimens were processed with proteinase K(3 ug/ml) over 30 minutes, they were reacted with EBER-1 probe and alkaline phosphatase-conjugated FITC antibody sequentially. In case 1, there were positive

hybridization signals corresponding to EBV transcripts(Fig. 4-A). In case 2, we could not find positive findings to EBV.

For the demonstration of the presence of EBV DNA in lesional tissue by Sourthern blot hybridization, the digested DNA was blotted onto a nylon membrane after digestion with Bam HI restriction endonuclease. The membrane was hybridized with probes of EBV Bam HI-A and -W fragments. In case 1, Southern blot hybridization showed a positive band at 3-kb in lesional tissue DNA when hybridized with the probe of Bam HI-W fragment and at 12-kb when hybridized with Bam HI-A fragment(Fig. 4-B). In case 2, there were no positive signals.

TCR(T cell receptor)-ß Gene Rearrangement Study

For the study of TCR-ß chain gene rearrangement, tumor DNA was digested with restriction endonuclease Bam HI, Eco RI, and Hind III, and was hybridized with a probe of constant region of TCR-ß gene(Cß). We could not demonstrate rearrangement findings in our cases because both cases showed germline patterns of TCR-ßgenes after analyses using the three endonucleases.

DISCUSSION

PTCL corresponding to our two cases is alternately called a post-thymic T-cell lymphoma bearing a mature T-cell phenotype, which shows significant geographic, clinical, histopathological, and prognostic diversity[6-9]. Although secondary PTCL is sometimes conceptualized to a separate fifth subgroup different from classical epidermotrophic T-cell lymphoma groups(mycosis fungoides, Sézary syndrome), Ki-1 +/- diffuse large T-cell lymphoma group, ACTCL group and HTLV-1+ ATL group[6,7], all these lymphomas are often included in PTCL in that PTCL essentially means a disease entity undergoing post-thymic T-cell maturation[3,8]. Accordingly, PTCL seems to be a greatly expanded lymphoma involving skin primarily or secondarily during disease processes[3,9]. In addition, PTCL is more common in Asia than in the Western world1[,9]. Our two cases belong to secondary PTCL according to the classifying mode by Su[3,8], because nodal involvement occurred primarily prior to the development of skin lesions.

It was shown that EBV was related to a spectrum of PTCL in addition to African Burkitt's lymphoma, nasopharyngeal cancer, Hodgkin's disease, thymic carcinoma and posttransplant B-cell lymphoma[1,10,11]. The detection of EBV viral genomes in tumor cell nuclei by in situ hybridization, latent membrane protein staining and Southern blot hybridization or PCR, was recently reported[8,11-13]. The association of EBV with PTCL such as nasal CD56+ PTCL, primary or secondary ACTCL and subcutaneous T-cell lymphoma, was demonstrated[8,11,13,14]. Although we could find EBV genomes in case 1, case 2 did not reveal EBV transcripts in tissue specimens.

Although PTCL is likely to disclose early extranodal involvement, a clinical course of PTCL in patients is extremely diverse according to histological grading, the positivity of Ki-1 antigen or HTLV-1 or EBV DNA in tumor tissues, and whether PTCL invades skin primarily or secondarily[6,8-10]. The clinical behavior of EBV-associated PTCL is usually fulminant with a median survival of only 6-8 months despite intensive chemotherapy[8,10-12,15,16]. Also the prognosis is significantly worse and systemic symptoms such as fever and hepatosplenomegaly are more frequent than that of EBV-negative PTCL[11,15]. This unique resistance to teatment and a worse clinical prognosis in EBV-associated PTCL are supposedly due to P-glycoprotein, a product of the multi-drug resistance gene(MDR-1)[1]. Our case 1 showed systemic symptoms and a fatal course compatible with EBV-associated PTCL. However, EBV-negative case 2 showed a relatively stable and indolent course without constitutional symptoms despite preceding nodal involvement.

Histologically, the biopsy findings that are commonly found in EBV-associated PTCL, are diffuse dermal infiltration of atypical lymphoid cells mainly along skin appendigeal and perivascular areas, angioinvasiveness and angiocentricity as in ACTCL, an aberrant expression of T-cell markers(e.g. loss of pan-T-cell markers as CD2, CD3 and CD7), features of hemophagocytosis, frequent epidermal necrosis and AILD[8,11,15-17]. In case 1, there were angiocentricity, angioinvasion, CD2/CD3 negativeness, marked hemophagocytotic findings, overlying epidermal necrosis and AILD. Angioinvasive atypical T cells in this case did not show typical glomeruloid concentric infiltrations around vessels that are invariably found in ACTCL. Although we found a dense lymphoid infiltrate in the subcutaneous fat in a biopsy specimen of case 1, there was no restrictively localized infiltrate in subcutis as in subcutaneous T-cell lymphoma[8]. In comparison with case 1, there were no hemophagocytotic histiocytes and epidermal necrotic findings in case 2 though we could observe angiocentricity, CD2/CD3 negativeness and AILD.

Reactive hemophagocytosis syndrome(RHS) is clinically characterized by a rapidly fatal course such as sustained fever and splenomegaly, blood pancytopenia, and a presence of histiocytes("bean-bag cells") phagocytizing hemopoietic cells in a bone marrow(>2%) and lesional tissues in PTCL[7,8,12,16]. RHS may occur when the lymphoma is in remission although most patients develop RHS at a time of an active stage of PTCL[12]. In this syndrome, the histiocytic activation is probably attributable to lymphokines such as γ-interferon, a tumor necrosis factor and interleukin-1 secreted by lymphoma cells[16]. A report suggests that EBV will upregulate the production of specific cytokines in T cells, accounting for the subsequent development of RHS[12]. In case 1, the concurrent findings of the patient as follows were diagnostic of RHS; a sustained fever, splenomegaly, pancytopenia, and a presence of hemophagocytizing histiocytes both in bone marrow and skin lesions. There was no RHS in , however, case 2.

Su et al[11] immunophenotypically subclassified EBV-associated PTCL into three categories as follows: 1) the helper type, CD4+ PTCL, 2) the cytotoxic/suppressor type, CD8+ PTCL, 3) ACTCL with no definable T cell subset. Although Nakamura et al[9,17,18] revealed that 50-60% of studied PTCL had showed a CD4+ phenotype without a survey for EBV positivity, there are recent reports of CD8+ EBV-associated PTCL, reflecting that CD8+ neoplastic T cells mainly contained the EBV genomes[11,15]. Both our cases revealed CD8+ lymphoid cells.

The plausibility that T-cell proliferations represent a reactive process to an EBV infection, might be excluded by the demonstration of clonal rearrangement of TCR-ß chain genes in tumor tissues11. However, the same observation of an absence of the TCR-ß gene rearrangement in PTCL as in our two cases, has been frequently reported[9-13]. Probably a T-γ/δlineage or undefined lineage of T cell subsets

or NK cells which express T cell antigens and does not have T cell antigen receptors, is proposed for these T cell neoplasms without TCR-ßgene rearrangement[11-13,16,18]. Accordingly, we could not exclude the palusibility that an absence of the TCR clonal rearrangement in our two cases might arise from the undefined cytogenic origin of neoplastic cells, whether abberrant T cell clones or NK cells.

In summary, we have demonstrated that EBV might determine the biological behavior of PTCL, in that the EBV positivity systematically demonstrable by serologic, molecular biologic and immunohistochemical methods, was closely related with the clinical course.

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