A Case Report of Diffuse Large B-Cell Lymphoma Associated with Epstein-Barr Virus in a Patient with Human Immunodeficiency Virus Infection

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ABSTRACT:

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Diffuse large B-cell lymphomas is the most frequent subtype of non-Hodgkin's lymphomas in both normal populations and human Immunodeficiency virus-infected individuals. Cutaneous involvement can be either primary or secondary. The common cutaneous features are erythematous to violaceous plaques, nodules, or ulcerative lesions. The histopathology typically demonstrates nodular or diffuse infiltration of large atypical lymphocytes with relatively sparing of the epidermis.

We reported a case of HIV infected woman presented with 2-month history of red-purplish rashes distributed all over the body including her face and oral cavity. She also had fever, night sweat, malaise, dysphagia, and significant weight loss. The skin biopsy showed diffuse dermal infiltration of medium to large atypical lymphocytes with epidermotropism. However, the immunohistochemistry demonstrated CD20-positive B lymphocytes in the vast majority of the infiltrating cells. The initial diagnosis was epidermotropic

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cutaneous B-cell lymphoma mimicking mycosis fungoides. Immunoblastic/activated B-cell subtype of diffuse large B-cell lymphoma was determined by further immunohistochemical study. In addition, Epstein-Barr virus was found obviously positive. According to the overall findings, we reported a case of diffuse large B-cell lymphoma associated with Epstein-Barr virus in a patient with human immunodeficiency virus infection.

Key words: Diffuse large B-cell lymphoma, epstein-barr virus infection, epidermotropism, human immunodeficiency virus infection

Case report

A 49-year-old Thai female, underlying chronic human Immunodeficiency virus (HIV) infection with poor adherence to antiviral drugs, presented with 2-month history of progressive mildly pruritic erythematous to violaceous rashes distributed all over the body including her face, chest, back, abdomen, and both upper extremities. Intraoral lesions were also observed. Moreover, she had experienced fever, night sweat, malaise, and significant weight loss of more than 10 kilograms within 2 months. Two months before the onset of the rash, the patient had nasal voice and dysphagia. Neck ultrasonography showed diffuse inflammation at bilateral thyroid glands, parotid glands, and submandibular glands with numerous lymph nodes, which were varying in size up to 3 cm at all level (I, II, III, IV, V). She also had anemia and received multiple blood transfusion. Her last CD4 count, 3 months before developing the rash, was 150 cells/μL.

Physical examination revealed multiple infiltrative erythematous to violaceous papules, plaques, and nodules on the face, chest, abdomen, back, and both upper extremities. Intraoral examination revealed infiltrative erythematous plaques on the alveolar ridge, soft, and hard palate. (Figure 1) Palpable cervical lymph nodes were also noted. According to clinical findings, a provisional diagnosis of a malignancy was considered.

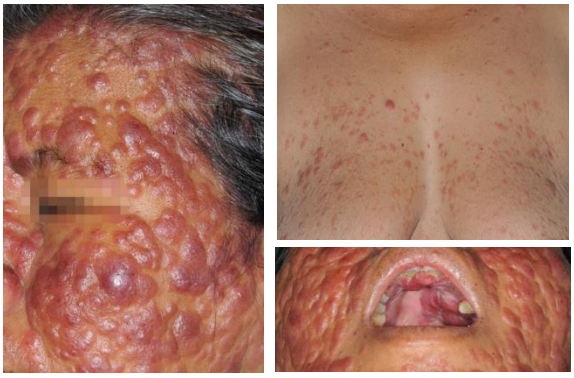

Figure 1 Multiple erythematous to violaceous papules, plaques, nodules were present on the face, oral cavity, and chest

Skin biopsy specimen was obtained from the right side of forehead. The histopathologic sections displayed a diffuse infiltration of medium to large cells with varying degree of atypia in the whole dermis, extending to subcutaneous fat, admixed with some reactive small lymphocytes,

and plasma cells. A focal area of necrosis was observed among inflammatory cells. Lining of atypical lymphocytes along dermoepidermal junction was noticed, compatible with epidermotropism. (Figure 2)

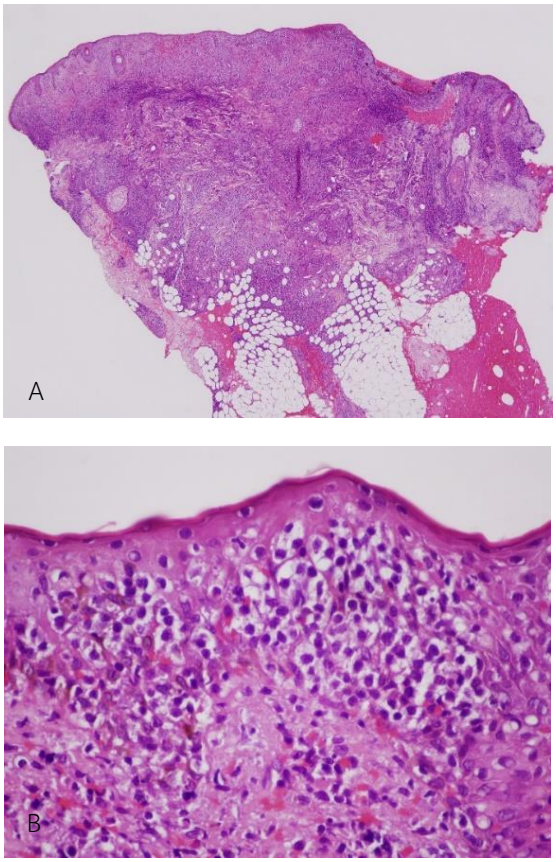

Figure 2 Skin biopsy specimen from right forehead with dense atypical lymphocytic infiltration in whole dermis and subcutaneous fat and focal area of epidermotropisim. (H&E; original magnification: A. X40, B. X600)

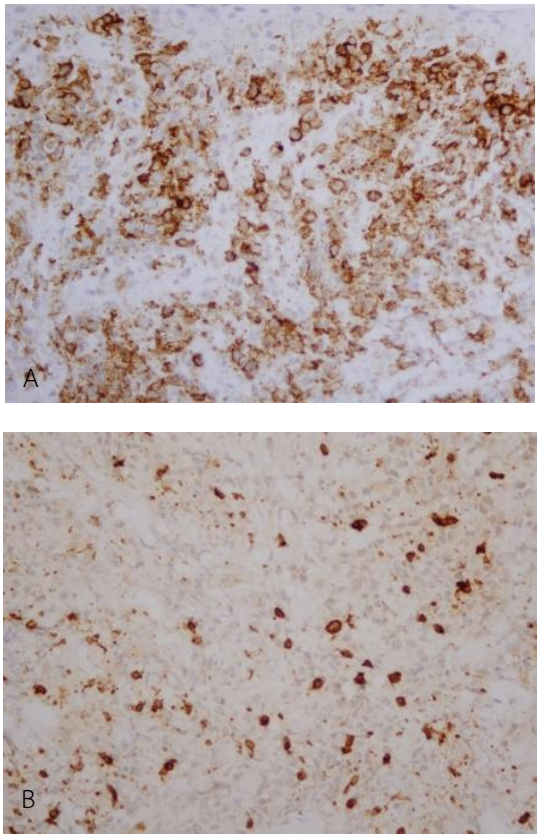

Figure 3 Immunohistochemical studies. A) CD20 stains the majority of the lymphocytes in the epidermis and dermis. B) A positive staining for CD3 in the reactive T cells

The immunohistochemical studies revealed minority of cells stained positively to T cell markers (CD3). But the vast majority of dermal cells as well as epidermotropic cells expressed CD20, suggesting the B-cell origin of the lesion. (Figure 3) Further immunohistochemical study revealed that majority of the cells were strongly positive to Bcl-2, MUM-1, and partially positive to CD30 and C-myc. Epstein-Barr virus was strongly

detected with nuclear staining pattern by in situ hybridization. Lack of expression of CD21, Bcl-6, HHV-8, and CD138 was noted. (Figure 4) The histopathological pattern is compatible with diffuse large B-cell lymphoma, immunoblastic/activated B-cell subtypes with EBV-positivity. Consequently, this patient was diagnosed with diffuse large B-cell lymphoma associated with Epstein-Barr virus in a patient with human immunodeficiency virus (HIV) infection. Further investigations to search for primary organ involvement and staging evaluation including computerized tomography scan of the chest, abdomen, and pelvis were planned. Unfortunately, the patient passed away before they were performed.

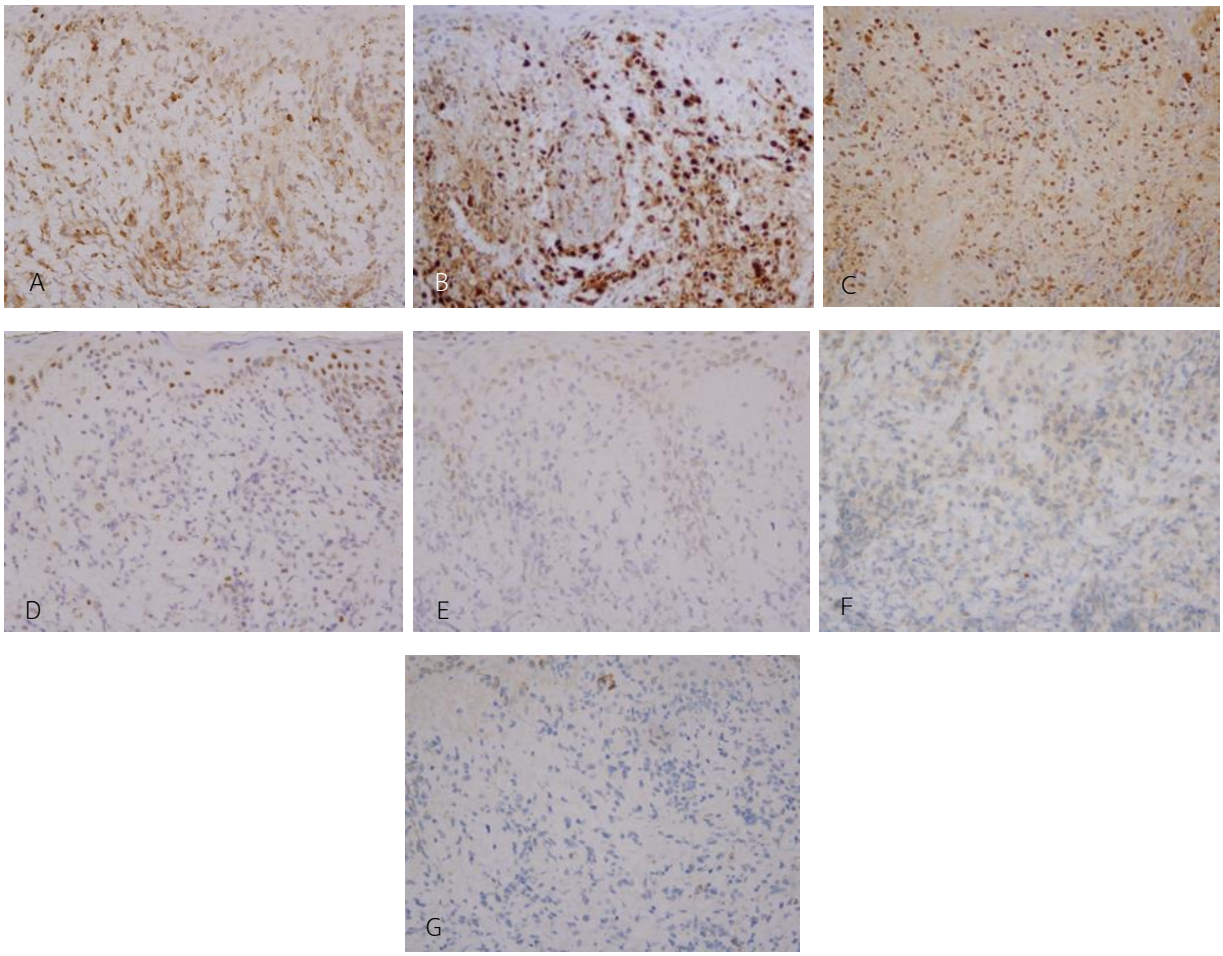

Figure 4 B-cell immunophenotype positive for (A) Bcl-2 (X400), (B) MUM-1 (X400), (C) EBV (X400, by in situ hybridization). The B-cell do not express (D) CD21 (X400), (E) Bcl-6 (X400), (F) HHV-8, (G) CD138 (X400)

Discussion

Systemic non-Hodgkin's lymphomas can have either primary or secondary skin involvement. The morphology and histology of primary and secondary cutaneous B-cell lymphomas are similar, but different in clinical course, prognosis, and treatment options[1]. Skin lesions generally presents as single or multiple red to violaceous papules, nodules, tumor, or infiltrative plaques, commonly located on the head and neck, or the extremities[2-4]. The histopathologic findings typically demonstrate diffuse dermal infiltration of large atypical lymphocytes with overlying Grenz zone[5]. Nevertheless, cutaneous B-cell lymphoma can have an unusual and rare manifestation with the presence of epidermotropism[6]. Hence, the appropriate immunohistochemical studies, for specific B-cell and T-cell markers is mandatory for the diagnosis of cutaneous lymphoma.

HIV-infected patients have a greater risk of developing non-Hodgkin lymphoma (NHL). The incidence is 60-200 times higher comparing to non-HIV patients[6]. The four main pathogenesis of HIV-related lymphomas are chronic antigen stimulation, genetic abnormalities, dysregulation of cytokines leading to high serum IL-6 and IL-10 levels, and the role of oncogenic viruses, EBV and HHV-8[7,8]. Over 90% of HIV-associated NHL is high grade B cells subtype and commonly have extranodal involvement[8]. Risk factors for developing aggressive B-cell NHL includes HIV viremia, nadir CD4 cell count, Epstein-Barr virus (EBV) exposure and degree of immunosuppression[9]. Around 15% to 20% of NHL cases show cutaneous involvement, and represent a clinical marker for advanced neoplasm. Cutaneous lesions can be the first manifestation of the disease in 5% to 10% of cases[10].

The most common lymphoma occurring in HIV-infected patients is diffuse large B-cell lymphoma (DLBCL)[11]. HIV-related DLBCL usually has clinical dissemination (stages III or IV) with extranodal involvement at the time of neoplasm diagnosis. The CNS, gastrointestinal tract, bone marrow, and liver are the most frequent organ involvement[8]. DLBCL occurring in HIV-infected patients is frequently associated with EBV compared with the DLBCL in general population[12].

The entity of EBV-positive DLBCL, NOS, usually occurs in patients aged > 50 years and lacks of a history of immunodeficiency or previous lymphoma[13]. DLBCL with EBV positivity arising in HIV-infected patients is a different entity, recognized as DLBCL associated with HIV infection[8].

Our patient has been diagnosed with advanced HIV disease with relatively low CD4 T cell counts at the time of lymphoma diagnosis. The clinical course was aggressive with rapid tumor involvement of the skin and the oral cavity.

Histopathologic sections showed diffuse infiltration of medium-sized to large lymphoid cells and immunohistochemical study was compatible with diffuse large B cell lymphoma in immunoblastic or activated B-cell subtypes with EBV-positivity. From clinicopathological correlation, the most likely diagnosis in this patient was diffuse large B-cell lymphoma associated with Epstein-Barr virus (EBV) in a patient with HIV infection.

There are 2 histologic subtypes of HIV-related DLBCL, including the centroblastic or germinal center B-cell subtype and immunoblastic or activated B-cell subtypes. The former subtype is more common and displays a diffuse sheet of large lymphoid cells with round to oval nuclei with prominent nucleoli. The tumor cells often express germinal center B-cell markers, such as CD10 and Bcl-6. While the latter subtype is composed of more than 90% immunoblasts with a feature of plasmacytoid differentiation. The tumor cells are post-germinal center derivation, which are positive for Bcl-2 but lack of CD10 and Bcl-6 expression. IRF4/MUM1 and CD138, which are markers of plasma cell derivation are frequently positive[7]. EBV positivity is found in about 30% of cases with HIV-related DLBCL[8]. The prognostic importance depends on patients' immune function and CD4 cell counts. Patients with severe immune suppression tend to have a higher incidence of immunoblastic subtypes, which have poorer outcome compared with the germinal center B-cell subtype. Moreover, MYC expression in HIV-positive patients with DLBCL is associated increase 2-year mortality[8]. Optimal timing of antiretroviral treatment with combination chemotherapy such as R-CHOP (rituximab and cyclophosphamide, doxorubicin, vincristine, prednisolone) should be considered according to patients' immune function and their performance status[7].

We reported a case of cutaneous B-cell lymphoma with histologically mimicking mycosis fungoides. The immunohistochemical study using antibodies to specific T-cell and B-cell markers can separate the two conditions and give the final diagnosis. This is a rare case of diffuse large B-cell lymphoma with EBV-positivity occurring in a setting of HIV infection with extensive cutaneous presentation and oral cavity involvement. Unfortunately, further investigation for systemic involvement could not be done. Based on the aggressive clinical course that had led to her death, systemic B-cell lymphoma with secondary cutaneous involvement was mostly considered.

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