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A Rare Case of Epstein-Barr Virus–Positive T-Cell Lymphoma in the Skin of an Immunocompromised Patient

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Abstract: Immunodeficiency-associated lymphoproliferative disorders are associated with latent infection by Epstein–Barr virus (EBV). Most cases of EBV-positive immunodeficiency-associated lymphoproliferative disorders arise from B cells, although some are of T-cell or natural killer origin. Cutaneous involvement is unusual and sporadically reported in the literature. We describe a rare case of an EBV-positive T-cell lymphoma presenting in the skin of a 32-year-old woman using adalimumab for neurosarcoidosis.

Key Words: Epstein–Barr virus, immunodeficiency, cutaneous T-cell lymphoma, adalimumab

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INTRODUCTION

Epstein-Barr virus (EBV)–related lymphoproliferative disorders (LPDs) occur in immunocompromised individuals, including those who use immunosuppressive medication. Most cases arise from B cells, and cutaneous localization is rare. Herein, we present a rare case of an EBV-associated lymphoproliferation of T-cell lineage that was initially discovered in the skin of a female patient using adalimumab—a tumor necrosis factor-alpha inhibitor—for neurosarcoidosis.

CASE REPORT

A 32-year-old woman presented to the dermatology outpatient clinic with 2, solitary, red–brown, heavily indurated, crusty plaques located on the trunk (Fig. 1). The plaques presented 1 month after increasing the dosage of adalimumab, which was started 11 months ago. In addition, a maculopapular rash was observed on the trunk, which presented 1 week after switching adalimumab to infliximab. A skin biopsy from the abdominal plaque demonstrated epidermal necrosis and a superficial and deep infiltrate consisting of histiocytes and small-to-medium–sized lymphocytes with an occasional aspect of larger blast cells and some nuclear pleomorphism (Figs. 2 and 3). Immunohistochemically, the infiltrate consisted of CD3-positive T-lymphocytes with retained expression of CD2 and CD4, whereas the expression of both CD5 and CD7 was lost. The infiltrate was positive for granzyme B but negative for T-cell intracellular antigen-1, CD30, CD56, myeloperoxidase, and PAX-5. The CD20 stain showed almost no admixture of B lymphocytes. The atypical infiltrate was positive for EBV-encoded messenger RNA (EBER), demonstrated by in situ hybridization (Fig. 4). T-cell receptor clonality analysis demonstrated a monoclonal T-cell population.

Additional examinations were planned for staging, including bone marrow biopsy and positron emission tomography–computed tomography (CT). In the meantime, however, the patient developed symptoms of extreme fatigue and difficult micturition along with dark-colored urine, for which she was admitted to the internal medicine inpatient ward. Blood examination showed anemia, thrombocytopenia, decreased haptoglobin levels, and greatly increased ferritin levels, consistent with a hemophagocytic syndrome associated with the EBV-positive T-cell lymphoma. Due to the urgent need for rapid diagnostic examination, CT was performed, which showed extensive systemic abnormalities suspicious of lymphoma localization, including in the lung, liver, adrenal, and renal parenchyma, diffusely in subcutaneous tissue, as well as thoracic and abdominal lymphadenopathy. The later performed positron emission tomography–CT confirmed this and showed additional evidence of lymphoma involvement in the orbit, spleen, bone marrow, cutis, muscles, and possibly also the heart. Bone marrow biopsy was positive for lymphoma involvement and hemophagocytosis. The EBV load in the plasma at this time was 239,000,000 copies per milliliter.

The patient underwent chemotherapy with CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and

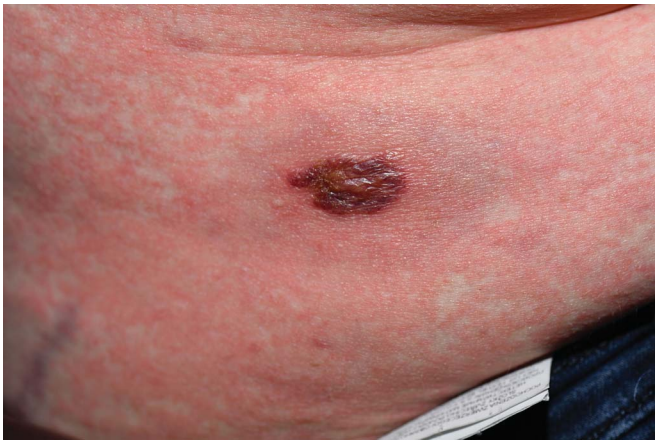

FIGURE 1. Dermatologic examination shows an indurated erythematous to brown-colored plaque on the trunk, with a subtle blue halo. The background shows the maculopapular rash induced by infliximab.

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The authors declare no conflicts of interest.

Written informed consent to use medical data for scientific research was obtained from the next of kin of the patient.

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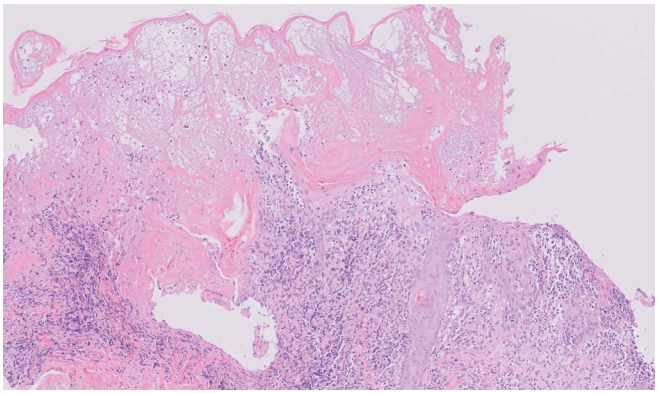

FIGURE 2. Skin biopsy of the abdominal lesion showing epidermal necrosis and a lymphohistiocytic infiltrate [hematoxylin and eosin stain, ×100].

prednisolone), resulting in a reduction of lymphoma lesions after 9 days of therapy. Unfortunately, during the course of CHOEP therapy, the patient developed cellulitis of the left upper leg and became septic. Despite extensive treatment with a variety of antibiotics, her situation deteriorated and she eventually died 4 weeks after the initial presentation. Autopsy was not performed.

DISCUSSION

Immunodeficiency is an important factor in the pathogenesis of LPDs. The World Health Organization distinguishes 4 categories of immunodeficiency-associated LPDs (IA-LPDs): posttransplant LPDs, lymphomas associated with HIV infection, LPDs associated with primary immune disorders, and other iatrogenic immunodeficiency-associated LPDs.[1] Methotrexate is the most common agent associated with LPDs, although other immunosuppressive agents have been reported, including thiopurines, tumor necrosis factor antagonists, and cyclosporine.[2,3] The case we reported here developed an LPD after increasing the dosage of adalimumab. The development of various types of LPDs in patients treated with adalimumab has been previously described in other case reports, including Hodgkin lymphoma,[4,5] mycosis fungoides,[6] cutaneous anaplastic large cell lymphoma,[7] EBV-associated plasmablastic lymphoma,[8] hepatosplenic T-cell lymphoma,[9] and adult T-cell leukemia/lymphoma.[10] However, none of those studies reported on an EBV-positive T-cell lymphoma in the skin.

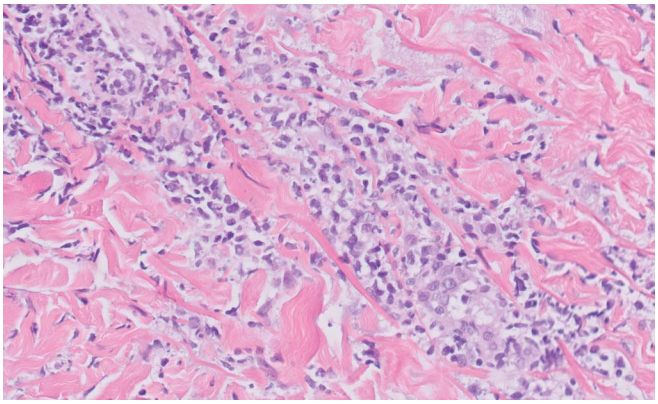

FIGURE 3. A close-up of the atypical infiltrate showing small-to-medium–sized lymphocytes with an occasional aspect of larger blast cells and some nuclear pleomorphism (hematoxylin and eosin stain, ×400).

EBV is an important malignant transformation factor in the pathogenesis of IA-LPDs. In the general population, primary EBV infection results in an immune response that usually presents as asymptomatic or subclinical disease in young children to infectious mononucleosis in adolescents and adults.[11] After primary infection with EBV, the virus establishes a lifelong latent infection in B cells, which is controlled by cytotoxic T cells. However, intensive immunosuppression may result in disturbances in this surveillance by T cells, leading to uncontrolled proliferation of EBV-infected B cells, thereby potentially resulting in malignant transformation.[12] Thus, most EBV-associated IA-LPDs are of B-cell origin. However, T-cell lymphomas are normally not associated with EBV and occur less in the setting of immunodeficiency. It is unknown how often EBV enters T cells, but rare T-cell lymphomas expressing EBV antigens have previously been described in the posttransplant setting, sometimes with localization in the skin.[13–17] In addition, Fardet et al [18] described the case of a large T-cell EBV-positive LPD in the skin of a 15-year-old boy diagnosed with AIDS. The use of adalimumab in our patient may add to the immune deficiency–related causes of EBV-positive T-cell LPDs. Although previous studies have discussed the use of immunosuppressive medication and its association with EBV-positive T-cell lymphomas, cutaneous involvement thereof was rarely reported.[19]

Although our patient used adalimumab, EBV-positive T-cell LPDs are not always associated with immunodeficiency. Differential diagnostic considerations include hydroa vacciniforme–like LPD (HV-LPD) and severe mosquito bite allergy—both cutaneous forms of chronic active EBV infection—as well as extranodal NK/T-cell lymphoma, nasal type, and angioimmunoblastic T-cell lymphoma. However, these entities contain several distinctive features not present in our case. For example, hydroa vacciniforme–like LPD normally occurs in sun-exposed skin, severe mosquito bite allergy is characterized by NK-cell lymphocytosis, extranodal NK/T-cell lymphoma, and nasal types are either from NK cell or $CD8^+$ T-cell lineage, and EBV-positive cells in angioimmunoblastic T-cell lymphoma are actually B cells within the T-cell proliferation.[20]

The exact mechanism that allows EBV to infect T cells remains undetermined. B-cell infection occurs via binding of gp350—a viral glycoprotein—to the complement receptor CD21 or (the more recently described) CD35,[21] in addition to attachment of viral gp42 to HLA class II.[22] Interestingly, previous studies reported on CD21 expression—albeit to a lesser extent—on peripheral T cells,[23,24] thymocytes,[25] and thymic emigrants,[26] which may account for T-cell infection by EBV and the lower incidence of EBV-associated T-cell LPDs in comparison to B-cell LPDs. In line, in a study using a neutralizing-antibody assay, both viral gp350 and CD21 were demonstrated to be required for infection of T cells by

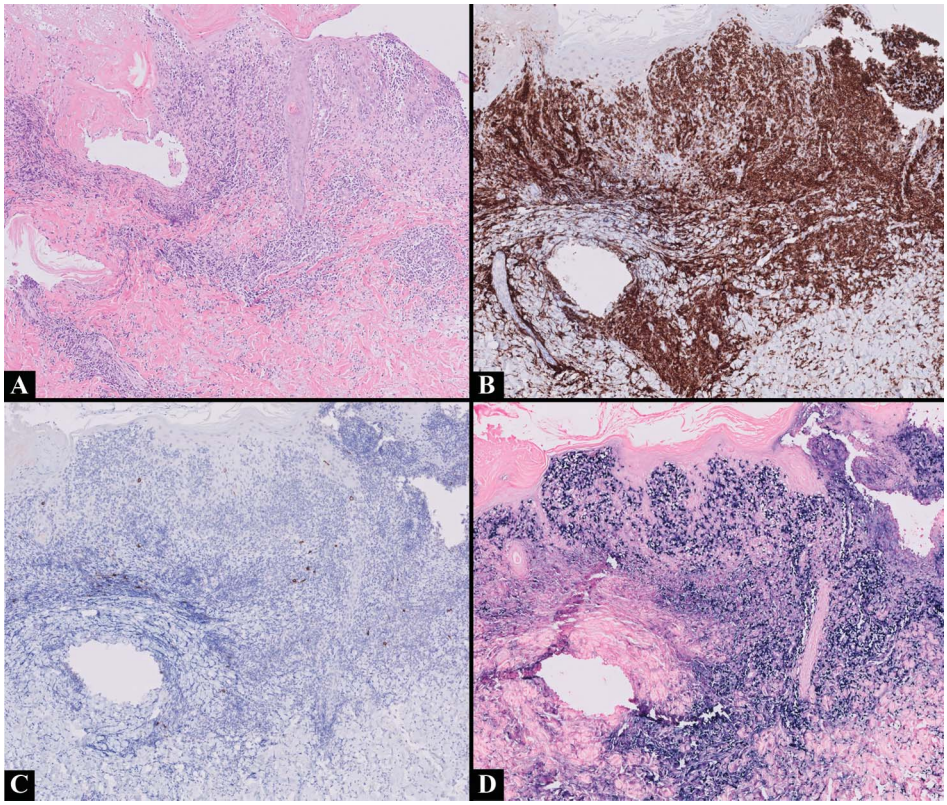

FIGURE 4. A, Close-up of the T-cell lymphoproliferation in the skin (hematoxylin and eosin stain, ×50). B, Immunohistochemistry for CD3 was positive in the lymphocytic infiltrate (CD3, ×50). C, Immunohistochemistry for CD20 showing almost no admixture of B lymphocytes (CD20, ×50). D, The atypical infiltrate was positive for EBER, demonstrated by in situ hybridization infiltrate (EBER, ×50).

EBV.[27] Above findings provide a potential mechanism involved in the development of the EBV-positive T-cell LPD in our patient.

To conclude, this is the first report describing an EBV-associated T-cell lymphoma with cutaneous involvement in a patient using adalimumab for neurosarcoidosis. Importantly, pathologists should become aware of this diagnostic possibility and similar cases may follow in the future.

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