Systemic Epstein-Barr Virus–Positive T-cell Lymphoma of Childhood

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PRACTICE **POINTS**

- Systemic Epstein-Barr virus (EBV)–positive T-cell lymphoma of childhood is a fulminant illness with a predilection for Asians and indigenous populations from Mexico and Central and South America. In most patients, the disease has an aggressive clinical course with high mortality.
- The disease often is complicated by hemophagocytic syndrome, coagulopathy, sepsis, and multiorgan failure. When these severe complications are absent, the prognosis might be better.
- In situ hybridization for EBV-encoded RNA and for T-cell receptor gene rearrangements is an important tool to establish the diagnosis as well as for treatment options and predicting the prognosis.

We report a case of a 7-year-old Chinese boy who presented with acute fever, multiple oral ulcers, and skin nodules. A diagnosis of systemic Epstein-Barr virus (EBV)–positive T-cell lymphoma of childhood was established using systemic laboratory examination, imaging studies, bone marrow and skin biopsy with immunohistochemistry, and in situ hybridization for EBV-encoded RNA (EBER) and gene rearrangements. Notable features of this case include the absence of pancytopenia and hemophagocytic syndrome as well as spontaneous resolution without chemotherapy for several months; however, the condition relapsed, and the patient died.

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Case Report

A 7-year-old Chinese boy presented with multiple painful oral and tongue ulcers of 2 weeks' duration as well as acute onset of moderate to high fever (highest temperature, 39.3°C) for 5 days. The fever was reported to have run a relapsing course, accompanied by rigors but without convulsions or cognitive changes. At times, the patient had nasal congestion, nasal discharge, and cough. He also had a transient eruption on the back and hands as well as an indurated red nodule on the left forearm.

Before the patient was hospitalized, antibiotic therapy was administered by other physicians, but the condition of fever and oral ulcers did not improve. After the patient was hospitalized, new tender nodules emerged on the scalp, buttocks, and lower extremities. New ulcers also appeared on the palate.

History—Two months earlier, the patient had presented with a painful perioral skin ulcer that resolved after being treated as contagious eczema. Another dermatologist previously had considered a diagnosis of hand-foot-and-mouth disease.

The patient was born by normal spontaneous vaginal delivery, without abnormality. He was breastfed; feeding, growth, and the developmental history showed no abnormality. He was the family's eldest child, with a healthy brother and sister. There was no history of familial illness. He received bacillus Calmette-Guérin and poliomyelitis vaccines after birth; the rest of the vaccine history was unclear. There was no history of immunologic abnormality.

Physical Examination—A 1.5×1.5-cm, warm, red nodule with a central black crust was noted on the left forearm (Figure 1A). Several similar lesions were noted on the buttocks, scalp, and lower extremities. Multiple ulcers, as large as 1 cm, were present on the tongue, palate, and left angle of the mouth (Figure 1B). The pharynx was congested, and the tonsils were mildly enlarged. Multiple enlarged, movable, nontender lymph nodes could be palpated in the cervical basins, axillae, and groin. No purpura or ecchymosis was detected.

Laboratory Results—Laboratory testing revealed a normal total white blood cell count (4.26×10^9/L

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The authors report no conflict of interest.

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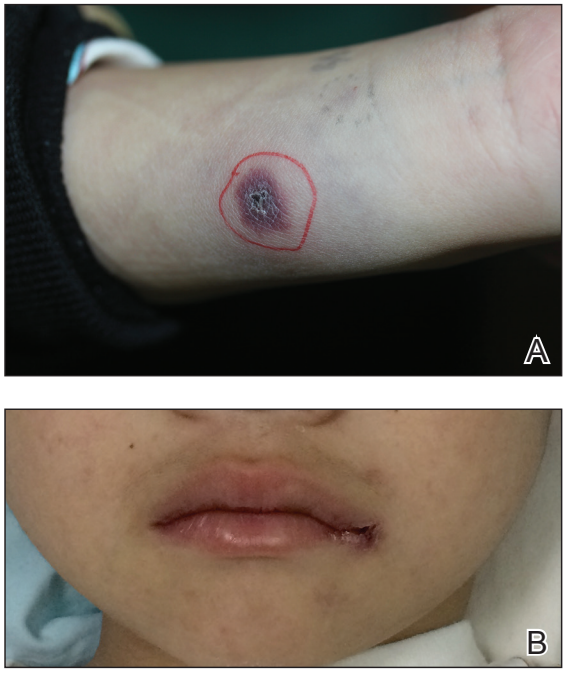

FIGURE 1. A, A 1.5×1.5-cm, dull, red nodule with a central black crust on the left forearm. B, An ulcer on the left angle of the mouth.

[reference range, 4.0–12.0×10^9/L]), with normal neutrophils (1.36×10^9/L [reference range, 1.32–7.90×10^9/L]), lymphocytes (2.77×10^9/L [reference range, 1.20–6.00×10^9/L]), and monocytes (0.13×10^9/L [reference range, 0.08–0.80×10^9/L]); a mildly decreased hemoglobin level (115 g/L [reference range, 120–160 g/L]); a normal platelet count (102×10^9/L [reference range, 100–380×10^9/L]); an elevated lactate dehydrogenase level (614 U/L [reference range, 110–330 U/L]); an elevated α-hydroxybutyrate dehydrogenase level (483 U/L [reference range, 120–270 U/L]); elevated prothrombin time (15.3 s [reference range, 9–14 s]); elevated activated partial thromboplastin time (59.8 s [reference range, 20.6–39.6 s]); and an elevated D-dimer level (1.51 mg/L [reference range, <0.73 mg/L]). In addition, autoantibody testing revealed a positive antinuclear antibody titer of 1:320 and a strong positive anti–Ro-52 level.

The peripheral blood lymphocyte classification demonstrated a prominent elevated percentage of T lymphocytes, with predominantly $CD8^+$ cells (CD3, 94.87%; CD8, 71.57%; CD4, 24.98%; CD4:CD8 ratio, 0.35) and a diminished percentage of B lymphocytes and natural killer (NK) cells. Epstein-Barr virus (EBV) antibody testing was positive for anti–viral capsid antigen (VCA) IgG and negative for anti-VCA IgM.

Smears of the ulcer on the tongue demonstrated gram-positive cocci, gram-negative bacilli, and diplococci. Culture of sputum showed methicillin-resistant *Staphylococcus aureus*. Inspection for acid-fast bacilli in sputum yielded negative results 3 times. A purified protein derivative skin test for *Mycobacterium tuberculosis* infection was negative.

Imaging and Other Studies—Computed tomography of the chest and abdomen demonstrated 2 nodular opacities on the lower right lung; spotted opacities on the upper right lung; floccular opacities on the rest area of the lung; mild pleural effusion; enlargement of lymph nodes on the mediastinum, the bilateral hilum of the lung, and mesentery; and hepatosplenomegaly. Electrocardiography showed sinus tachycardia. Nasal cavity endoscopy showed sinusitis. Fundus examination showed vasculopathy of the left retina. A colonoscopy showed normal mucosa.

Histopathology—Biopsy of the nodule on the left arm showed dense, superficial to deep perivascular, periadnexal, perineural, and panniculitislike lymphoid infiltrates, as well as a sparse interstitial infiltrate with irregular and pleomorphic medium to large nuclei. Lymphoid cells showed mild epidermotropism, with tagging to the basal layer. Some vessel walls were infiltrated by similar cells (Figure 2). Infiltrative atypical lymphoid cells expressed CD3 and CD7 and were mostly $CD8^+$, with a few $CD4^+$ cells and most cells negative for CD5, CD20, CD30, CD56, and anaplastic lymphoma kinase. Cytotoxic markers granzyme B and T-cell intracellular antigen protein 1 were scattered positive. Immunostaining for Ki-67 protein highlighted an increased proliferative rate of 80% in malignant cells. In situ hybridization for EBV-encoded RNA (EBER) demonstrated EBV-positive atypical lymphoid cells (Figure 3). Analysis for T-cell receptor (TCR) γ gene rearrangement revealed a monoclonal pattern. Bone marrow aspirate showed proliferation of the 3 cell lines. The percentage of T lymphocytes was increased (20% of all nucleated cells). No hemophagocytic activity was found.

Diagnosis—A diagnosis of systemic EBV-positive T-cell lymphoma was made. Before the final diagnosis was made, the patient was treated by rheumatologists with antibiotics, antiviral drugs, nonsteroidal anti-inflammatory drugs, and other symptomatic treatments. Following antibiotic therapy, a sputum culture reverted to normal flora, the coagulation index (ie, prothrombin time, activated partial thromboplastin time) returned to normal, and the D-dimer level decreased to 1.19 mg/L.

The patient's parents refused to accept chemotherapy for him. Instead, they chose herbal therapy only; 5 months later, they reported that all of his symptoms had resolved; however, the disease suddenly relapsed after another 7 months, with multiple skin nodules and fever. The patient died, even with chemotherapy in another hospital.

Comment

Prevalence and Presentation—Epstein-Barr virus is a ubiquitous γ-herpesvirus with tropism for B cells, affecting more than 90% of the adult population worldwide. In addition to infecting B cells, EBV is capable of infecting T and NK cells, leading to various EBV-related lymphoproliferative disorders (LPDs). The frequency and clinical presentation of infection varies based on the type of EBV-infected cells and the state of host immunity.[1-3]

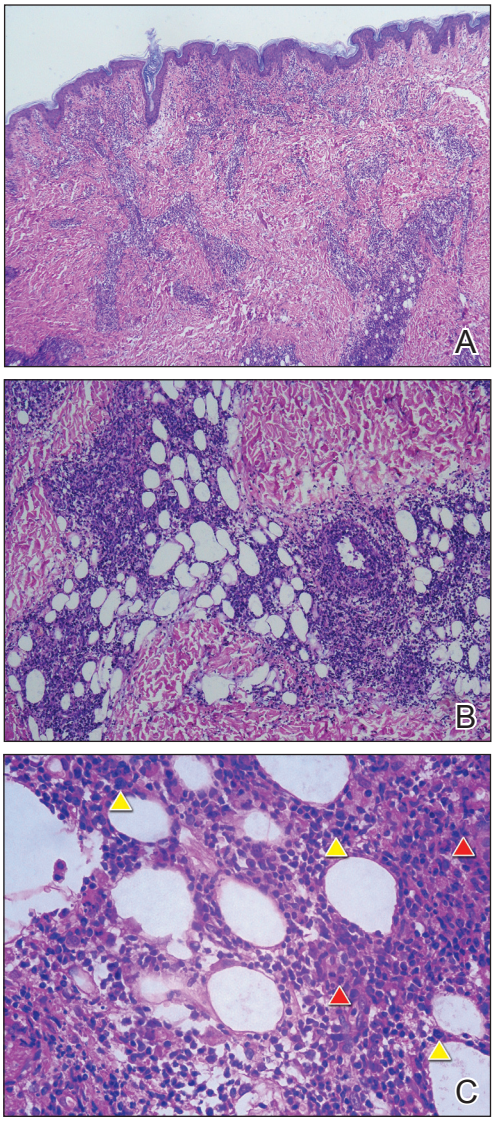

FIGURE 2. Histopathology showed dense, superficial to deep perivascular and sparse interstitial lymphoid infiltrate. A, Lymphoid cells were mildly epidermotropic (H&E, original magnification ×40). B, Panniculitislike changes were evident in fat tissue, and a vessel wall was infiltrated by the lymphoid cells (H&E, original magnification ×100). C, Infiltrative cells were irregular, pleomorphic, and medium to large with mild atypia. Scattered atypical mitotic figures were identified. Yellow arrowheads pinpoint atypical lymphoid cells with irregular nuclear contour; red arrowheads pinpoint atypical mitoses (H&E, original magnification ×400).

Primary infection usually is asymptomatic and occurs early in life; when symptomatic, the disease usually presents as infectious mononucleosis (IM), characterized by polyclonal expansion of infected B cells and subsequent cytotoxic T-cell response. A diagnosis of EBV infection can be made by testing for specific IgM and IgG antibodies against VCA, early antigens, and EBV nuclear antigen proteins.[3,4]

Associated LPDs—Although most symptoms associated with IM resolve within weeks or months, persistent or recurrent IM-like symptoms or even lasting disease occasionally occur, particularly in children and young adults. This complication is known as chronic active EBV infection (CAEBV), frequently associated with EBV-infected T-cell or NK-cell proliferation, especially in East Asian populations.[3,5]

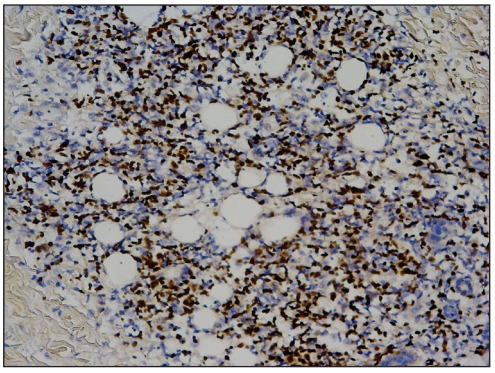

FIGURE 3. In situ hybridization showed infiltrative cells positive for Epstein-Barr virus–encoded RNA (original magnification ×200).

Epstein-Barr virus–positive T-cell and NK-cell LPDs of childhood include CAEBV infection of T-cell and NK-cell types and systemic EBV-positive T-cell lymphoma of childhood. The former includes hydroa vacciniforme–like LPD and severe mosquito bite allergy.[3]

Systemic EBV-Positive T-cell Lymphoma of Childhood—This entity occurs not only in children but also in adolescents and young adults. A fulminant illness characterized by clonal proliferation of EBV-infected cytotoxic T cells, it can develop shortly after primary EBV infection or is linked to CAEBV infection. The disorder is rare and has a racial predilection for Asian (ie, Japanese, Chinese, Korean) populations and indigenous populations of Mexico and Central and South America.[6-8]

Complications—Systemic EBV-positive T-cell lymphoma of childhood is often complicated by hemophagocytic syndrome, coagulopathy, sepsis, and multiorgan failure. Other signs and symptoms include high fever, rash, jaundice, diarrhea, pancytopenia, and hepatosplenomegaly. The liver, spleen, lymph nodes, and bone marrow are commonly involved, and the disease can involve skin, the heart, and the lungs.[9,10]

Diagnosis—When systemic EBV-positive T-cell lymphoma occurs shortly after IM, serology shows low or absent anti-VCA IgM and positive anti-VCA IgG. Infiltrating T cells usually are small and lack cytologic atypia; however, cases with pleomorphic, medium to large lymphoid cells, irregular nuclei, and frequent mitoses have been described. Hemophagocytosis can be seen in the liver, spleen, and bone marrow.[3,11]

The most typical phenotype of systemic EBV-positive T-cell lymphoma is $CD2^+CD3^+CD8^+CD20^-CD56^-$, with expression of the cytotoxic granules known as T-cell intracellular antigen 1 and granzyme B. Rare cases of $CD4^+$ and mixed $CD4^+/CD8^+$ phenotypes have been described, usually in the setting of CAEBV infection.[3,12] Neoplastic

cells have monoclonally rearranged TCR-γ genes and consistent EBER positivity with in situ hybridization.[13] A final diagnosis is based on a comprehensive analysis of clinical, morphological, immunohistochemical, and molecular biological aspects.

Clinical Course and Prognosis—Most patients with systemic EBV-positive T-cell lymphoma have an aggressive clinical course with high mortality. In a few cases, patients were reported to respond to a regimen of etoposide and dexamethasone, followed by allogeneic hematopoietic stem cell transplantation.[3]

In recognition of the aggressive clinical behavior and desire to clearly distinguish systemic EBV-positive T-cell lymphoma from CAEBV infection, the older term *systemic EBV-positive T-cell LPD of childhood*, which had been introduced in 2008 to the World Health Organization classification, was changed to *systemic EBV-positive T-cell lymphoma of childhood* in the revised 2016 World Health Organization classification.[6,12] However, Kim et al[14] reported a case with excellent response to corticosteroid administration, suggesting that systemic EBV-positive T-cell lymphoma of childhood may be more heterogeneous in terms of prognosis.

Our patient presented with acute IM-like symptoms, including high fever, tonsillar enlargement, lymphadenopathy, and hepatosplenomegaly, as well as uncommon oral ulcers and skin lesions, including indurated nodules. Histopathologic changes in the skin nodule, proliferation in bone marrow, immunohistochemical phenotype, and positivity of EBER and TCR-γ monoclonal rearrangement were all consistent with systemic EBV-positive T-cell lymphoma of childhood. The patient was positive for VCA IgG and negative for VCA IgM, compatible with systemic EBV-positive T-cell lymphoma of childhood occurring shortly after IM. Neither pancytopenia, hemophagocytic syndrome, nor multiorgan failure occurred during the course.

Differential Diagnosis—It is important to distinguish IM from systemic EBV-positive T-cell lymphoma of childhood and CAEBV infection. Detection of anti–VCA IgM in the early stage, its disappearance during the clinical course, and appearance of anti-EBV–determined nuclear antigen is useful to distinguish IM from the neoplasms, as systemic EBV-positive T-cell lymphoma of childhood is negative for anti-EBV–determined nuclear antigen. Carefully following the clinical course also is important.[3,15]

Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis can occur in association with systemic EBV-positive T-cell lymphoma of childhood and might represent a continuum of disease rather than distinct entities.[14] The most useful marker for differentiating EBV-associated hemophagocytic lymphohistiocytosis and systemic EBV-positive T-cell lymphoma of childhood is an abnormal karyotype rather than molecular clonality.[16]

Outcome—Mortality risk in EBV-associated T-cell and NK-cell LPD is not primarily dependent on whether the lesion has progressed to lymphoma but instead is related to associated complications.[17]

Conclusion

Although systemic EBV-positive T-cell lymphoma of childhood is a rare disorder and has race predilection, dermatologists should be aware due to the aggressive clinical source and poor prognosis. Histopathology and in situ hybridization for EBER and TCR gene rearrangements are critical for final diagnosis. Although rare cases can show temporary resolution, the final outcome of this disease is not optimistic.

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