Primary cutaneous Epstein-Barr virus–related lymphoproliferative disorders in 4 immunosuppressed children

Nadège Wallet-Faber, MD,[a] Christine Bodemer, MD,[b] Stéphane Blanche, MD,[c] Eric Delabesse, MD,[d] Catherine Eschard, MD,[e] Nicole Brousse, MD,[a] and Sylvie Fraitag, MD[a]
Paris, Toulouse, and Reims, France

Primary cutaneous Epstein-Barr virus–related lymphoproliferative disorders are rare. We describe 4 cases in children: two with acquired immunodeficiencies (HIV infection, heart transplantation) and two with congenital immunodeficiencies (ataxia-telangiectasia and an undetermined disease affecting the T lymphocytes). Two of the lymphoproliferative disorders were T-cell types and two were B-cell types. The two T-cell types were also Epstein-Barr virus positive, which is extremely rare. Three of the patients developed extracutaneous disease with poor outcome, resulting in death. (J Am Acad Dermatol 2008;58:74-80.)

Epstein-Barr virus (EBV)-related lymphoproliferative disorders (LPD) occur in immunodeficient individuals and are frequently localized in extranodal sites, although they rarely affect the skin. This also includes posttransplantation LPD (PTLD), recognized as a significant complication of organ transplantation. In most cases monomorphic EBV-related LPD are of B-cell type and are linked to an abnormal outgrowth of EBV-transformed B lymphocytes, whereas T-cell LPD are a rare occurrence.[1] We describe 4 particularly rare pediatric cases of EBV-related LPD, which were apparent through cutaneous involvement. The clinical, pathologic, immunophenotypic, and genotypic findings are discussed within the context of the literature currently available on these disorders.

Abbreviations used:

EBER: Epstein-Barr virus–encoded early RNA
EBV: Epstein-Barr virus
ISH: in situ hybridization
LMP: latent membrane protein
LPD: lymphoproliferative disorders
PCR: polymerase chain reaction
PTLD: posttransplantation lymphoproliferative disorders
TCR: T-cell receptor

All 4 patients were given diagnoses from 1995 to 2005. Data regarding their medical condition, treatments, and outcome were obtained by reviewing the patient's records. Multiple skin biopsy specimens were analyzed. We obtained paraffin-embedded tissue and fresh-frozen tissue for 3 patients (patients 1, 2, and 4) and only paraffin-embedded tissue for one (patient 3). The 4-mm punch biopsy specimens of the skin were fixed in formalin and processed for light microscopy; 5-μm sections were stained with hematoxylin and eosin. Immunohistochemical studies were performed on 3-μm sections using a standard streptavidin-biotin-peroxidase method with the antibodies listed in Table I.

In situ hybridization (ISH) was carried out on formalin-fixed paraffin-embedded tissue sections using an EBV-encoded early RNA (EBER) oligonucleotide synthetic probe (DakoCytomation, Glostrup, Denmark) following the manufacturer's protocol.

Polymerase chain reaction (PCR) was performed on DNA extracted from fresh-frozen tissue. T-cell receptor (TCR)γ and IgH gene clonality assays were

From the Departments of Pathology,[a] Dermatology,[b] and Pediatric Immunology and Hematology,[c] Groupe Hospitalier Necker Enfants-Malades, Assistance Publique-Hôpitaux de Paris, Université Paris-Descartes, Paris; Laboratory of Hematology, INSERM U563, Hôpital Purpan, CHU Toulouse, Université Paul-Sabatier[d]; and Department of Dermatology, CHU Reims, Hôpital Robert Debré, Reims.[e]
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Reprint requests: Nadège Wallet-Faber, MD, Department of Pathology, Groupe Hospitalier Necker-Enfants Malades, 149 rue de Sèvres, 75743 Paris cedex 15, France. E-mail: nadegewallet@club-internet.fr.
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Table I. Antibodies used (immunohistochemistry)

	Antigen recognized (CD)	Reactivity (preferential) or cells identified	Dilution	Source
L26	CD20	B cells	1/200	Dako, Glostrup, Denmark
CD3	CD3	T cells	1/250	Dako, Glostrup, Denmark
OPD4	CD4	T cells (helper/inducer)	1/100	Becton Dickinson, San Jose, Calif
BerH2	CD30	R-S-activated lymphocytes	1/50	Immunotech, Beckman Coulter, Marseille, France
LMP1	EBV latent membrane protein 1	EBV latent infected cells	1/100	Dako, Glostrup, Denmark
Ki67	Nuclear antigen	Normal proliferating cells labeling index in tumors	1/100	Dako, Glostrup, Denmark
P80	Alk protein	Some cases of ALCL, T-cell type	1/50	Dako, Glostrup, Denmark
CD56 (NCAM)	CD56	NK cells and subset of activated T lymphocytes	1/100	Novocastra, Newcastle, United Kingdom
TiA1		Cytotoxic cells	1/100	Immunotech, Beckman Coulter, Marseille, France
Granzyme B		Cytotoxic cells	1/50	Novocastra, Newcastle, United Kingdom
KP1	CD68	Histiocytes	1/1500	Dako, Glostrup, Denmark

ALCL, Anaplastic large cell lymphoma; *EBV*, Epstein-Barr virus; *LMP1*, latent membrane protein; *NCAM*, neural cell adhesion molecule.

performed as described by Brumpt et al[2] and Landman-Parker et al,[3] respectively.

CASE REPORTS

Case 1

Fardet et al[4] described this case previously. A boy was given the diagnosis of AIDS at 12 years of age. He did not receive any treatment. At age 15 years he developed a firm purplish inflammatory extranodal 2- × 3-cm nodule in right axilla suggestive of Kaposi's disease. A skin biopsy specimen of the nodule showed a diffuse, perivascular, and periadnexal infiltrate extending through the whole dermis and the subcutaneous tissue, and mainly constituted of large lymphocytes with large pleomorphic nuclei and prominent nucleoli (Fig 1, *A*). Many cells were necrosed. Immunohistochemical studies revealed a strong positivity of proliferative cells for CD3 (Fig 1, *B*), CD4, and CD30 and negativity for CD8, CD20, P80, and CD68. Many of the atypical cells showed EBV-associated antigen latent membrane protein (LMP) 1. Moreover, ISH for EBV transcripts EBER showed intense nuclear reactivity in the nucleus of more than 80% of the tumoral cells (Fig 1, *C*). TCR rearrangement by PCR demonstrated that the lymphoid population was monoclonal. No other sites of lymphoproliferation were identified. The patient was highly immunodeficient with an absolute CD4 count lower than 5/mm^3.

The nodule was removed surgically then treated with radiotherapy. The combination of this local treatment and an antiretroviral multitherapy treatment made the nodule disappear completely. The CD4 count progressively increased to more than 300/mm^3 and plasma HIV1 RNA levels rapidly decreased to an undetectable level. Two years later the patient relapsed (Fig 1, *D*). Through questioning we discovered that the patient had stopped the antiretroviral therapy. He was treated again and, after local radiotherapy in combination with an effective antiretroviral therapy, a total regression of this new lesion was observed. Currently, 8 years later, the patient is still receiving antiretroviral therapy and there is no new cutaneous nodule.

Case 2

A girl with dilated primitive cardiomyopathy underwent orthotopic heart transplantation when she was 1 year old. The immunosuppressive regimen consisted of cyclosporin A and azathioprine. Four years after the transplantation, at age 5 years, she developed a fever and hepatosplenomegaly. Serologic testing for EBV positively revealed anti—early antigen and anti—virus capsid antigen IgG, which is the characteristic pattern of a previously occurred infection. PCR quantification of the EBV viral load was positive (1/100^e). The patient was followed up 1 year later when she developed an only necrotic nodule on the forehead and a pharyngolaryngeal infiltration, which caused breathing difficulties. A pathologic examination of the cutaneous nodule revealed a dense nodular and interstitial lymphoid infiltrate, which extended through the whole dermis (Fig 2). It mainly constituted small