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Aggressive Peripheral CD70-positive T-cell Lymphoma Associated with Severe Chronic Active EBV Infection

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Abstract

Severe chronic active Epstein-Barr virus infection (CAEBV) in T or NK cells is a rare complication of latent EBV infection. CAEBV associated T-cell lymphoproliferative disease (LPD) consists of polyclonal lesions as well as aggressive lymphomas. Here we report such a patient. In addition, we show that this primary CAEBV associated T-cell lymphoma expresses CD70 and is sensitive to killing by CD70-specific T cells, identifying CD70 as a potential immunotherapeutic target for CAEBV-associated T-cell lymphoma.

Keywords

EBV; CD70; Lymphoma; Immunotherapy

INTRODUCTION

Severe chronic active Epstein-Barr virus infection (CAEBV) is a rare complication of latent EBV infection. It occurs predominately in Japan but several cases have been reported in the western hemisphere [1, 2]. In CAEBV natural killer (NK), T cells, or rarely B cells are infected, predisposing patients to life-threatening complications, such as hemophagocytic

syndrome and NK- or T-cell lymphoproliferative disease (LPD) [3, 4]. CAEBV-associated LPD includes more benign, polyclonal lesions as well as aggressive lymphomas. It has been suggested that indolent NK- or T-cell LPDs subsequently evolve into aggressive lymphoma; however, there are only a few examples documenting the progressive transformation of polymorphic LPD to an aggressive monomorphic lymphoma [5]. Here we report a patient, who developed an aggressive CD70-positive T-cell lymphoma in the setting of CAEBV.

CASE REPORT

The patient, a 4 year old Vietnamese male, initially presented with fever, lymphadenopathy, and splenomegaly. A lymph node biopsy (post prednisone) was non-diagnostic and he was diagnosed with T-cell CAEBV by having no evidence of autoimmune disease or underlying immunodeficiency, symptoms for greater 3 months, elevated EBV-IgG (>1:10,420) and EBV-EA (1:640), elevated EBV-DNA load of greater 100,000 EBV genome copies per μg of DNA (gc/ μg DNA), EBV predominantly present in his T-cell compartment, and a T-cell clone in his peripheral blood as detected by T-cell receptor gene rearrangements. He was treated with decadron, etoposide, and cyclosporine resulting in a transient decline of his EBV-DNA load from 124,154 to 9,628 gc/ μg DNA. Three months after diagnosis he underwent a myeloablative syngeneic hematopoietic stem cell transplant from his unaffected twin.

Within 3 months post transplant he had recurrent disease as judged by increasing EBVDNA load and development of persistent left-sided cervical lymphadenopathy. He received donor lymphocytes, donor-derived EBV-specific cytotoxic T cells (CTLs), and 2 doses of donor-derived LMP2-specific CTLs on a published Phase I/II clinical study [6]. Post CTL infusions his EBV-DNA load decreased from 5,491 to 1,649 gc/ μg DNA. His EBV-DNA load then slowly increased to 7,465 gc/ μg DNA when he had a cervical lymph node biopsy, which was consistent with a polymorphous T-cell LPD. Immunophenotyping demonstrated a predominance of CD4-positive/CD7-negative T cells, which were strongly positive for EBV by in situ hybridization (EBER) with only occasional LMP1-positivity (Figures 1A–D). Molecular diagnostic studies demonstrated clonal T-cell receptor gene rearrangement. His EBV-DNA load continued to increase, ranging from 35,514 to 275,343 gc/ μg DNA, despite receiving 1 dose of donor lymphocytes and 4 additional doses of LMP2-specific CTLs.

One month after his last CTL infusion he presented with fever, pancytopenia, and recurrent left cervical lymphadenopathy. A repeat biopsy revealed similar findings to the previous biopsy (Figure 1E), and clonality studies showed the presence of the same T-cell clone. He was treated with a short course of prednisone and remained in good clinical condition until 4 months later when he presented with increasing left cervical lymphadenopathy. At that time his EBV-DNA load was 111,694 gc/ μg DNA. A repeat biopsy revealed more aggressive features with complete lymph node effacement and the presence of occasional atypical Reed-Sternberg like cells (Figure 1F). T cells were EBV-positive and immunophenotyping revealed the same CD4-positive/CD7-negative T-cell population with evidence of clonality as judged by T-cell receptor gene rearrangement. At this time a second hematopoietic stem cell transplant was considered, but no closely matched alternate donor could be identified.

Eight months after his last biopsy he presented with a large inguinal mass. A biopsy demonstrated an aggressive peripheral T-cell lymphoma (Figures 1G–I). There was a diffuse population of large abnormal EBER-positive T cells that expressed CD4 with aberrant loss of pan T-cell markers CD5, surface CD3, and CD7. Cytogenetics revealed an abnormal karyotype [46, XY, del(7)(q31)]. The patient received chemotherapy (etoposide, methylprednisolone, cytarabine), however died 14 days after starting chemotherapy of

rapidly progressive disease and treatment related complications, including *Staph. aureus* sepsis.

CD70 is the membrane bound ligand of CD27, which belongs to the tumor necrosis factor receptor superfamily [7]. We have shown that CD70 is expressed in EBV-positive NK/T-cell lymphoma cell lines and that T cells, genetically engineered to express a CD70-specific chimeric antigen receptor (CAR) recognize and kill CD70-positive cell lines [8]. Figure 2A shows that the primary T-cell lymphoma of this CAEBV patient expressed CD70. In addition, CD70-specific, donor derived T cells killed primary CD70-positive T-cell lymphoma cells in a standard cytotoxicity assay whereas non-transduced T cells did not (Figure 2B).

DISCUSSION

Differentiating T-cell CAEBV, X-linked lymphoproliferative disease (XLP), and EBV-associated hemophagocytic lymphohistiocytosis (HLH) remains a challenge. In this regard, determining in which lymphocyte compartment EBV predominately resides might be instructive. While EBV resides in B cells in XLP, in T-cell CAEBV it is present in T cells. EBV-associated HLH was excluded since this patient had normal NK function, no evidence of hemophagocytosis, and a normal ferritin level at presentation. While genetic tests for XLP- and HLH-associated gene defects were not routinely available at the time of the patient's diagnosis, we would recommend that such tests are performed nowadays during the initial diagnostic work up.

The proposed classification system for CAEBV-related LPD includes three categories: 1) polymorphic LPD without clonal proliferation of EBV-infected cells, 2) polymorphic LPD with clonality, and 3) monomorphic LPD (T or NK cell lymphoma/leukemia) with clonality [9]. The initial biopsy was consistent with the second category, whereas the last biopsy was consistent with the third. According to the new 2008 WHO classification the patient's biopsies were consistent with systemic EBV-positive T-cell LPD of childhood [10].

Current treatment protocols for CAEBV rely on chemotherapy followed by hematopoietic stem cell transplant [11–15]. Survival rates vary between 50–95% with better outcomes for patients, who are less than 8 years old at diagnosis, have fewer complications pretransplant, and received a reduced intensity conditioning transplant [11–15]. While stem cell transplant currently remains the only curative options for patients with CAEBV, immunotherapy may become an alternative. Polyclonal T cells specific for EBV antigens or enriched for the EBV-encoded LMP2 antigen have been used successfully to treat EBV-associated malignancies and this patient was enrolled on a study using LMP2-specific T cells [6]. While he had a prolonged partial response, his disease eventually progressed. Besides targeting EBV antigens, genetically modifying T cells with CARs, which target non-EBV antigens, is one attractive strategy to redirect T cells to CAEBV-associated T-cell lymphomas [16]. However, few potential tumor-associated antigens have been identified for T-cell malignancies. CD70 is aberrantly expressed on a broad range of malignancies including, HTLV-1-associated T-cell lymphoma/leukemia, and EBV-associated malignancies [17–19]. We had previously shown that EBV-positive NK/T-cell lines express CD70 [8]. We now demonstrate that CD70 is expressed in primary CAEBV-associated T-cell lymphoma cells, and that these cells are sensitive to killing by CD70-specific T cells, identifying CD70 as a potential immunotherapeutic target for CAEBV-associated T-cell lymphoma.

In summary, this case report highlights the progressive nature of CAEBV associated T-cell LPD. Hematopoietic stem cell transplant is at present the only curative option and should be considered in all T-cell CAEBV patients before they develop aggressive lymphoma.

Acknowledgments

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Figure 1. Progressive transformation to aggressive T-cell lymphoma

Representative section of lymph node biopsies are shown from 2nd (A–D), 3rd (E), 4th (F), and 5th biopsy (G–I). A, B, E, F, G: H&E stain. F: inset highlights atypical Reed-Sternberg like cells; C, H: CD3 immunohistochemistry; D, I: EBER in situ hybridization. All pictures taken at 400× magnification except 1A (200× magnification).

Figure 2. CD70-specific T cells kill primary CD70-positive CAEBV-associated T-cell lymphoma
A: C70 expression in T-cell lymphoma as judged by FACS analysis. **B:** Donor-derived, syngeneic CD70-specific T cells were generated according to published methods [8]. While CD70-specific T cells killed CD70-positive target cells (patient lymphoma, K562.CD70), CD70-negative cells (K562) were not killed. Non-transduced T cells (NT T cells) had no cytolytic activity against all 3 target cells.