

BRIEF REPORT

Epstein Barr Virus Induced Lymphoma in a Child With IPEX Syndrome

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IPEX syndrome (immune deficiency, polyendocrinopathy, enteropathy, X-linked) is a disorder of regulatory T cell (Treg) function which can result in early death due to infection or complications related to autoimmunity. Therapeutic options for these patients can include allogeneic stem cell transplantation (SCT) or the use of

immunosuppressive regimens to control the manifestations of autoimmunity. We report a patient with IPEX syndrome who was managed with rapamycin and subsequently developed EBV induced lymphoma. *Pediatr Blood Cancer*
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Key words: Epstein Barr virus; immunodeficiency; IPEX syndrome; lymphoma; rapamycin

INTRODUCTION

Recent reports have demonstrated that patients with IPEX syndrome can be successfully transplanted using a submyeloablative approach, minimizing peri-transplant morbidity and mortality [1,2]. However some patients with IPEX respond well to a course of immunosuppressive therapy, which can control the autoimmune manifestations of this disease [3]. We report a child for whom transplant was not logistically practical for the family and who was placed on rapamycin, and subsequently developed Epstein Barr virus (EBV) induced lymphoma. This case demonstrates the difficult decisions made in selecting therapy for these patients.

CASE

This subject was a full term male child born to parents from Puerto Rico, with no prenatal or post-natal complications. His brother, who also has IPEX, underwent a submyeloablative SCT using an unrelated cord blood donor at 6 years of age, following the development of recurrent severe infections, failure to thrive, autoimmune enteritis and recurrent laryngeal papillomas [1]. Our patient presented at 3 months of age with failure to thrive, lower gastrointestinal tract hemorrhage and an eczematoid rash. His white blood cell count was $36,000 \text{ mm}^{-3}$ with 15% eosinophils with an otherwise a normal WBC differential, hemoglobin was 10.2 g/dl, and his platelet count was $22,000 \text{ mm}^{-3}$. He had an absolute CD4 count of $4,784 \text{ mm}^{-3}$ and his CD19 count was $5,020 \text{ mm}^{-3}$, but phytohemagglutinin, concanavalin A, and pokeweed mitogen stimulation assays were below the 10th percentile. IgG level was 257 mg/dl, IgM was <20 mg/dl, and IgA was <10 mg/dl. Despite resolution of his gastrointestinal hemorrhage and thrombocytopenia, he continued to have failure to thrive, with culture negative diarrheal stools, and developed aphthous stomatitis. A diagnosis of IPEX was made based on sequencing data showing a mutation in exon 10 of the FOXP3 gene (Dr. Troy Torgerson, Fred Hutchinson Cancer Research Center).

Due to recent reports of clinical improvement in IPEX patients with rapamycin [3], as well as practical difficulties for his parents caring for two SCT recipients simultaneously, our patient was started on rapamycin 0.1 mg/kg/day at 1.5 years of age. Within 1 month of starting rapamycin, he had improvement in his eczema, a decrease in his diarrheal stools (although he continued to have poor weight gain), and improvement in his aphthous stomatitis. Eight months after starting rapamycin he presented with fever and tender cervical lymphadenopathy. A blood culture was positive for

streptococcus viridans and coagulase negative staphylococcus, but despite broad spectrum antibiotics he developed progression of his lymphadenopathy as well as abdominal pain. CT scan revealed diffuse lymphadenopathy of the neck, mediastinum and hilar areas, with bilateral parenchymal densities in the lungs. A biopsy of one of his cervical lymph nodes revealed a clonal (kappa light chain), monomorphous, diffuse large B cell lymphoma (CD20 positive), which was positive for EBV by in situ hybridization for EBER, but quantitative EBV PCR from his peripheral blood was not elevated. Rapamycin was discontinued and a course of anti-CD20 monoclonal antibody therapy ($375 \text{ mg/m}^2/\text{week}$) was started. Despite three doses of anti-CD20 monoclonal antibody he had further progression of his lymphadenopathy and developed bloody stools. Due to concerns regarding his abdominal process he was taken to surgery, and a biopsy of his affected small bowel revealed lymphoma. Due to progression of his lymphoma and the development of respiratory compromise, he received cyclophosphamide $600 \text{ mg/m}^2/\text{day}$ every 21 days for three doses and VCR 0.05 mg/kg weekly for four doses and achieved a clinical and radiographic complete response, as well as complete resolution of his rash and stomatitis. He continues to have poor weight gain, requiring parenteral nutrition, and plans are underway for an allogeneic stem cell transplant.

DISCUSSION

The defective gene for IPEX syndrome, FOXP3, is responsible for Treg development, encoding the forkhead box P3 transcription factor [4–6]. Dysfunction in Treg leads to autoimmunity, which results in the clinical findings seen in IPEX patients [7]. While FOXP3 mutations have been reported to result in Treg impairment in several patients with IPEX syndrome, some subjects may not have a detectable mutation in the FOXP3 coding region [6]. Most patients

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Received 13 June 2007; Accepted 17 July 2007

with IPEX develop autoimmune manifestations of their disease during the first 3 months of life with the most common being enteropathy, diabetes mellitus, failure to thrive, hemolytic anemia, eczema, autoimmune thrombocytopenia and lymphadenopathy [7–9]. Causes of death vary for these patients, but can be due to hemorrhage, sepsis, or due to complications of diabetes mellitus. Neither our patient nor his brother had endocrine manifestations of autoimmunity; however, both had severe autoimmune enteritis and infection.

Due to the poor long-term prognosis for IPEX patients [7], therapies have involved either systemic immunosuppression to control autoimmune manifestations of disease, or allogeneic SCT. While the latter can be curative, the use of myeloablative regimens are associated with a high risk of morbidity and mortality in this patient population [10,11]. Recently we and other groups have reported successfully transplanting patients with IPEX using a submyeloablative conditioning regimen [1,2]. Bindl et al. [3] reported the use of rapamycin in three patients with IPEX, and one subject maintained a remission for over 5 years of rapamycin and methotrexate. The other two patients had marked improvement in their enteropathy, skin manifestations and a decrease in the incidence of infections, as did our patient.

The use of rapamycin is clearly associated with improvement in the autoimmune manifestations of this disease, but little is known about the long-term risks associated with the use of this agent in IPEX patients. Rapamycin binds to FKBP12, which complexes with the mammalian target of rapamycin (mTOR), and this complex inhibits a ribosomal enzyme (p70s6 kinase), resulting in inhibition of proliferation [12]. Although this drug has an anti-proliferative effect on B cells, rapamycin is a potent immunosuppressive agent, and like other similar medications could make some of these subjects at high risk for development of EBV induced lymphoproliferation. The development of EBV lymphoma in our patient could have been as a result of a primary EBV infection, which in the setting of systemic immunosuppression and a baseline poor level of lymphocyte function made this infection difficult to control. This patient's brother developed asymptomatic EBV reactivation following his allogeneic SCT, likely as a result of immunosuppression to treat graft versus host disease. Immunosuppressive therapy remains a reasonable option for IPEX patients with a less severe phenotype and who lack appropriately matched stem cell donors. This report highlights the fact that the use of systemic immunosuppression can render a subset of IPEX patients to be at high risk for

EBV induced lymphoma. IPEX patients who present with fever or lymphadenopathy while on rapamycin should be evaluated for this disorder.

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