Cerebral Lymphoma in an Adenosine Deaminase–Deficient Patient With Severe Combined Immunodeficiency Receiving Polyethylene Glycol–Conjugated Adenosine Deaminase

David A. Kaufman, MD*; Michael S. Hershfield, MD‡; Joseph A. Bocchini, MD*; I. John Moissidis, MD*; Majed Jeroudi, MD*; and Sami L. Bahna, MD, DrPH*

ABSTRACT. Polyethylene glycol–conjugated adenosine deaminase (PEG-ADA) provides an alternate therapy to mismatched stem cell transplantation for patients with ADA-deficient severe combined immunodeficiency. Although replacement therapy with PEG-ADA is effective in preventing infections, immune function does not return to normal, and most patients remain lymphopenic. Information is limited regarding the prognosis of patients on long-term ADA-replacement therapy. Here we present a case of a 10-year-old child who was diagnosed with ADA-severe combined immunodeficiency at 4 weeks of age after contracting pneumonia. Treatment with PEG-ADA was begun, the biochemical markers of ADA deficiency normalized, and his clinical progress was very good without significant infections. At 10 years of age, after presenting with headaches and cranial nerve deficits, he was diagnosed with Epstein-Barr virus–positive malignant brain lymphoma. It did not respond to various regimens of aggressive chemotherapy, and the patient expired 5 months later. We speculate that in this patient the immunologic surveillance by T cells may have been defective with respect to elimination of Epstein-Barr virus–infected cells, hence the formation of neoplasm. The possible mechanisms underlying such pathology are reviewed. *Pediatrics* 2005;116:e876–e879. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-1068; *immunodeficiency, severe combined immunodeficiency, ADA deficiency, PEG-ADA, lymphoma.*

ABBREVIATIONS. SCID, severe combined immunodeficiency; ADA, adenosine deaminase; EBV, Epstein-Barr virus; PEG, polyethylene glycol; BMT, bone marrow transplant; dAXP, erythrocyte deoxyadenosine nucleotides; Ig, immunoglobulin.

Severe combined immunodeficiency (SCID) is a lethal childhood disease. One of its subtypes is caused by adenosine deaminase (ADA) deficiency secondary to mutations in the gene coding for the enzyme. The absence of functional ADA enzyme leads to the accumulation of toxic metabolites and other effects that impair lymphocyte differentiation, viability, and function, resulting in combined immunodeficiency.[1,2]

Lymphoproliferative disorders, usually related to Epstein-Barr virus (EBV), may develop in individuals with certain types of primary immunodeficiencies, including SCID. Polyethylene glycol–conjugated bovine ADA (PEG-ADA) is a replacement therapy for ADA deficiency.[3,4] PEG prolongs the half-life of the ADA enzyme by reducing its catabolism. By greatly reducing the levels of toxic metabolites, PEG-ADA therapy has been successful in preventing infections, although restoration of immune function is only partial. Information regarding the long-term prognosis of patients receiving PEG-ADA is limited. Here we report the case of a boy who received PEG-ADA for 10 years with effective control of infections but ultimately developed cerebral lymphoma.

CASE REPORT

A 10-year-old white male who was being followed at our allergy/immunology clinic for ADA-SCID and had been doing well on PEG-ADA (Adagen; Enzon, Inc, Piscataway, NJ) therapy presented to his pediatrician because of a 6-week history of headache, eye deviation, and weakness. The headache was increasingly severe, constant, and localized to the left frontotemporal area. There was no aura, and the pain was unrelated to positional change. Increasing dose and frequency of nonsteroidal antiinflammatory drugs had been ineffective for pain relief. For the previous few weeks, he had a decreased appetite and an ~10-lb weight loss. One week before presentation, his right eye appeared medially deviated, and his right upper and lower extremities became weak. His pediatrician noticed no fever or nuchal rigidity and transferred him to our hospital.

He was the family's firstborn as a term infant. At 4 weeks of age, he developed severe pneumonia, and an immunologic evaluation at another academic institution revealed ADA-SCID with red-cell ADA activity of 0.5 nmol/hour per mg protein (~1% of normal). His ADA genotype was Ala83→Asp in exon 4 of one allele and a 5′ splice junction mutation + 1 Gly→Ala in exon 5 of his second ADA allele.[5]

A matched bone marrow transplant (BMT) donor could not be found, and the patient's family declined mismatched BMT, preferring ADA-replacement therapy. With the initiation of PEG-ADA therapy, plasma ADA activity increased by ~100- to 1000-fold, and the level of erythrocyte deoxyadenosine nucleotides (dAXP) fell from 0.806 μmol/mL packed cells at diagnosis to 0 to 0.01 μmol/mL (normal: <0.002 μmol/mL) (Fig 1). These values were maintained throughout the subsequent 10-year period of therapy. His lymphocyte count increased to 702 to 1200 cells per mm^3. He progressed very well without any significant infections and had satisfactory growth and development; hence, he was not tested for lymphocyte proliferation responses, although the results

From the *Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, Louisiana; and ‡Department of Biochemistry, Duke University Medical Center, Durham, North Carolina.

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Address correspondence to Sami L. Bahna, MD, DrPH, Department of Pediatrics, Allergy/Immunology Section, Louisiana State University Health Sciences Center, 1501 Kings Hwy, Shreveport, LA 71130–3239. E-mail: sbahna@lsuhsc.edu
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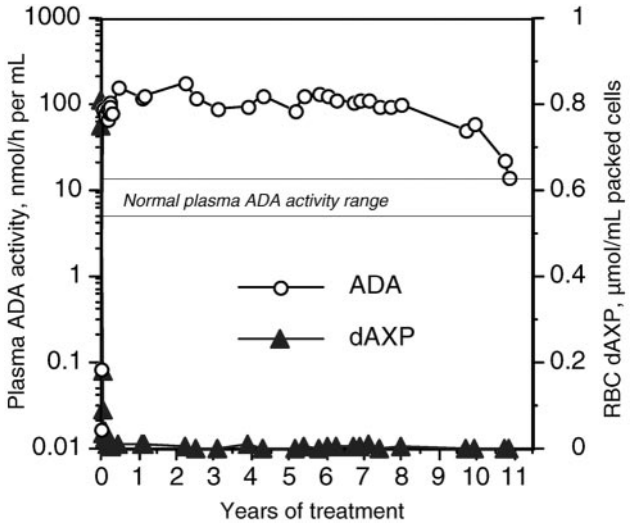

Fig 1. Plasma ADA activity and dAXP concentration. RBC indicates red blood cell.

would have been of interest. Intravenous immunoglobulin (Ig) therapy was discontinued at 4 years of age, and his serum Ig levels were maintained at normal values (IgG: 885–1170 mg/dL; IgA: 58–67 mg/dL; IgM: 30–31 mg/dL; IgE: 47 IU/mL). At age 6, he had a brief hospitalization after varicella exposure, which was uneventful.

At the time of the most recent illness, the patient's medications included 500 U of PEG-ADA intramuscularly twice per week (27 U/kg per week) and prophylactic trimethoprim/sulfamethoxazole 80/400 mg 3 days per wk. He also received dextroamphetamine/amphetamine 20 mg/day for attention-deficit/hyperactivity disorder. The patient was in the fourth grade, with good performance. A younger half-brother was in good health. There was no family history suggestive of immunodeficiency.

The child appeared mildly ill but was alert and oriented. His temperature was 98.8°F, his heart rate was 84 beats per minute, his respiratory rate was 22 per minute, and his blood pressure was 105/76 mm Hg. His weight was 36 kg (75th percentile), and his height was 137 cm (50th percentile). His right eye was noticeably deviated medially. The pupils were equal, round, and reactive to light bilaterally, and the visual fields were intact. Fundoscopic examination revealed bilateral papilledema. There was no nuchal rigidity or cervical lymphadenopathy. Lung and heart auscultation was normal. There were no masses, organomegaly, or abdominal tenderness. Neurologic examination revealed right-eye medial deviation, indicating a cranial nerve VI deficit. There was also right-sided facial paralysis, indicating a cranial nerve VII deficit. The strength of the right extremities in all muscle groups was 4/5. A right-sided pronator drift was noted. Superficial and deep sensations were intact.

A complete blood cell count revealed a leukocyte number of 5100/mm^3 (75% polymorphonuclear leukocytes, 6% lymphocytes, 17% monocytes, and 2% eosinophils), hemoglobin level of 12.8 g/dL, hematocrit level of 36.6%, and platelet count of 356 000/mm^3. A comprehensive metabolic profile was within normal limits, including C-reactive protein level of 0.11 mg/dL, lactate dehydrogenase level of 141 U/L, and uric acid level of 1.9 mg/dL.

MRI of the brain revealed 2 enhancing, irregular, ovoid lesions with hypointense centers surrounded by vasogenic edema: 1 in the left frontoparietal region (32 × 32 mm) and 1 in the left occipital region (23 × 30 mm) (Fig 2). Open brain biopsy of both lesions demonstrated malignant lymphoma, large-cell type, with immunoblastic and plasmacytoid features. Immunophenotyping showed an atypical lymphoid population that expressed CD10, CD19, and CD45 without CD34 expression, suggesting malignant B-cell lymphoma, large-cell phenotype. Fluorescent in situ hybridization showed deletions in chromosomes 1p36, 19q13, and 10q23, but BCL6 analysis was normal. The results of bacterial, viral, and fungal cultures were negative, as was staining for acid-fast bacilli. The biopsy specimen revealed high anti-EBV antibody titers of both IgG (>170 U) and IgM (134 U) isotypes.

Initial treatment with dexamethasone and phenytoin began, and he was transferred to St Jude Children's Research Hospital (Memphis, TN) for specialized treatment. Chemotherapy was initiated with the COP (cyclophosphamide, vincristine, and prednisone) regimen, but after 1 week his lesions showed no response. He was switched to the APO (doxorubicin, vincristine, 6-MP, and prednisone) regimen, but he experienced progressive right-arm weakness, and follow-up imaging showed enlargement of the lymphoma. He then was started on methotrexate in a high dose. After 4 weeks, an intracranial abscess developed; it was evacuated, and multiple antibiotics were administered. Despite continued antibiotic therapy, the patient expired ~5 months after the discovery of the lymphoma.

DISCUSSION

SCID can be inherited either in an X-linked or autosomal recessive fashion. The latter has at least 6 genetic subtypes, of which ADA deficiency is the most common and is associated with the most profound depletion of T, B, and natural killer cells.[6] ADA deficiency is found in ~15% of all SCID cases. Clinically, these patients present with symptoms similar to other types of SCID, including early onset of recurrent opportunistic infections, candidiasis, diarrhea, and failure to thrive. Although the consequences of immunodeficiency usually lead to symptoms within the first few months of life, some patients may not present until late childhood or adulthood.[7] Other clinical manifestations may be present in patients with ADA-SCID, although they are not pathognomonic. Osseous abnormalities occur in 50% of patients, including cupping and flaring of the costochondral junctions, pelvic dysplasia, shortened vertebral transverse processes with end-point convexity, and thick growth-arrest lines.[8] Abnormalities of the liver, kidney, or adrenal glands have been noted on autopsy.[9] Central nervous system dysfunction may be more common in ADA-SCID than in other types of SCID.[10]

There is a good correlation between ADA genotype, the degree of enzyme deficiency based on expression of mutant ADA cDNA, the level of dAXP, and clinical severity as indicated by age at diagno-

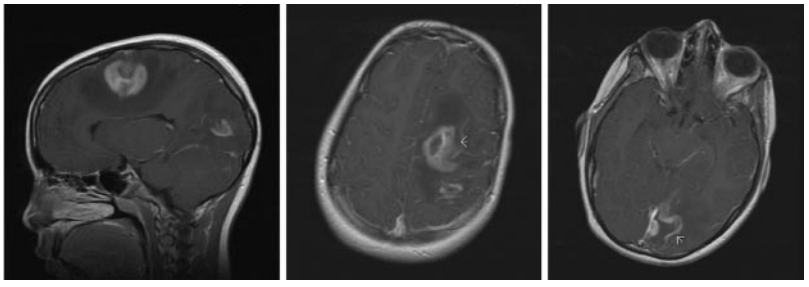

Fig 2. MRI showing lesions in the left frontoparietal and occipital regions.

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sis.[7,11] Our patient's genotype and his markedly elevated dAXP are consistent with his presentation at 4 weeks of age with pneumonia and immunologic abnormalities typical of early-onset SCID. The patient did not have an HLA-identical stem cell donor and was treated by enzyme replacement. Therapy with PEG-ADA resulted in sustained correction of dAXP elevation in erythrocytes and control of infection. Although the lymphocyte count increased, it remained at a lymphopenic level.

Although it is not curative, PEG-ADA is tolerated well and has resulted in survival comparable with or better than survival with stable engraftment reported for ADA-deficient patients who have received HLA-mismatched stem cell transplants. The experience in 119 patients treated with PEG-ADA since it entered clinical trial in 1986 (it was approved by the US Food and Drug Administration in 1990) through 2002 has been reviewed.[2] Among 76 patients who were still receiving PEG-ADA, 30 (39%) had been on therapy for >5 years, including 21 (28%) who had been treated for 10 to 15 years. Because PEG-ADA does not restore normal immune function and the total number of patients treated beyond 5 years is small, the long-term outlook for such patients is not known with certainty.

In addition to our patient, we are aware of 2 others who have developed lymphoproliferative disorders while on PEG-ADA.[2] One girl developed an EBV-positive pulmonary nodule after 8 years, and a boy developed Hodgkin's lymphoma after being on PEG-ADA for 13 years (a younger ADA-deficient sibling of the boy died of lymphoma in early childhood after undergoing haploidentical BMT[12]). Both of these patients eventually died after attempted BMT.

A higher incidence of lymphoproliferative disorders has been noted in children with various types of primary immunodeficiency diseases[13] such as ataxia-telangiectasia (10% of cases), Wiskott-Aldrich syndrome (7.6%), and common variable immunodeficiency (1.4–7%) and occasionally in hyper-IgM syndrome and X-linked lymphoproliferative syndrome.[14–16] In SCID, the incidence of neoplasia is 1% to 5%, with ~74% being non-Hodgkin's lymphomas.[13]

The notion that the incidence of lymphoproliferative disease in patients with immunodeficiency is significantly higher has been known for >30 years.[17] Lymphoproliferative disorders in both acquired and congenital immunodeficiency share several characteristics including origination in or involvement of extranodal sites, diffuse aggressive histologic characteristics, B-cell lineage, association with EBV, and usually rapid progression.[18] All such traits were noticed in our patient. In a series of 19 patients with lymphoproliferative disorders and immunodeficiency, polymorphic forms were the most common.[19] Six patients had malignant lymphoma, with the most frequent type being diffuse large B-cell non-Hodgkin's lymphoma. The latter was noted in our patient.

The pathogenesis of lymphoproliferative diseases in primary immunodeficiency is believed to involve the interplay of 3 factors: polyclonal activation of lymphoid proliferation; abnormal regulation of the lymphoid proliferation by the dysfunctional immune system; and chromosomal abnormalities.[20] In a general sense, EBV infection contributes to the first factor by modulating apoptotic signals and cytokine balances in B cells without insulting the host, leading to lymphocyte proliferation.[21] EBV seems also to suppress the T-cell surveillance function.[22] In a retrospective analysis, 1.2% of post–hematopoietic stem cell transplant patients developed B-cell lymphoproliferative disease.[23] Therefore, immune reconstitution, in general, does not preclude the development of lymphoproliferative disorders.

CONCLUSIONS

This case illustrates an excellent response to ADA-replacement therapy regarding infection control, yet it was complicated by the development of EBV-positive malignant lymphoma that was resistant to therapy and was rapidly fatal. Similar cases have been reported even in patients after immune reconstitution by stem cell transplantation. It seems that chronic EBV infection plays an important role in enhancing the development of lymphoproliferative disease in immune-deficient patients.

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