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TREATMENT OF X-LINKED LYMPHOPROLIFERATIVE DISEASE (DUNCAN DISEASE) WITH HIGH-DOSE METHYLPREDNISOLONE AND ETOPOSIDE (VP-16)*

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A five-year-old boy in the acute phase of X-linked lymphoproliferative (XLP) syndrome (Duncan disease) with high fever and hepatosplenomegaly was treated successfully with high-dose methylprednisolone and VP-16 for 15 months. He had been alive for four years after diagnosis as of this writing. We recommend high-dose methylprednisolone and VP-16 in patients with XLP who have to wait for a suitable donor before bone marrow transplantation. *Key words: X-linked lymphoproliferative disease, high-dose methylprednisolone, VP-16, treatment.*

Purtilo et al.[1] described a fatal X-linked condition which affected 18 males in four generations in 1975. This condition is known as X-linked lymphoproliferative disease (XLP) or Duncan disease. XLP is a lethal disease associated with a lack of effective immune response to Epstein-Barr virus (EBV). One half of the patients with XLP have developed infectious mononucleosis (IM). Unfortunately most of the cases with infectious mononucleosis died[1-3]. Various therapeutic agents have been tried unsuccessfully in XLP patients experiencing acute EBV infection[4,5]. Here we report a patient with XLP treated with high-dose methylprednisolone and etoposide (VP-16), and we comment on two of his relatives who were also affected by XLP.

Case Reports

Case 1

In 1991, a two-year-old boy was admitted to Hacettepe Children's Hospital with a three-week history of fever. He was the third product of a marriage between first cousins. Six boys in the family, including his brother had died between the ages of 1.5 and four years with similar clinical pictures (Fig. 1).

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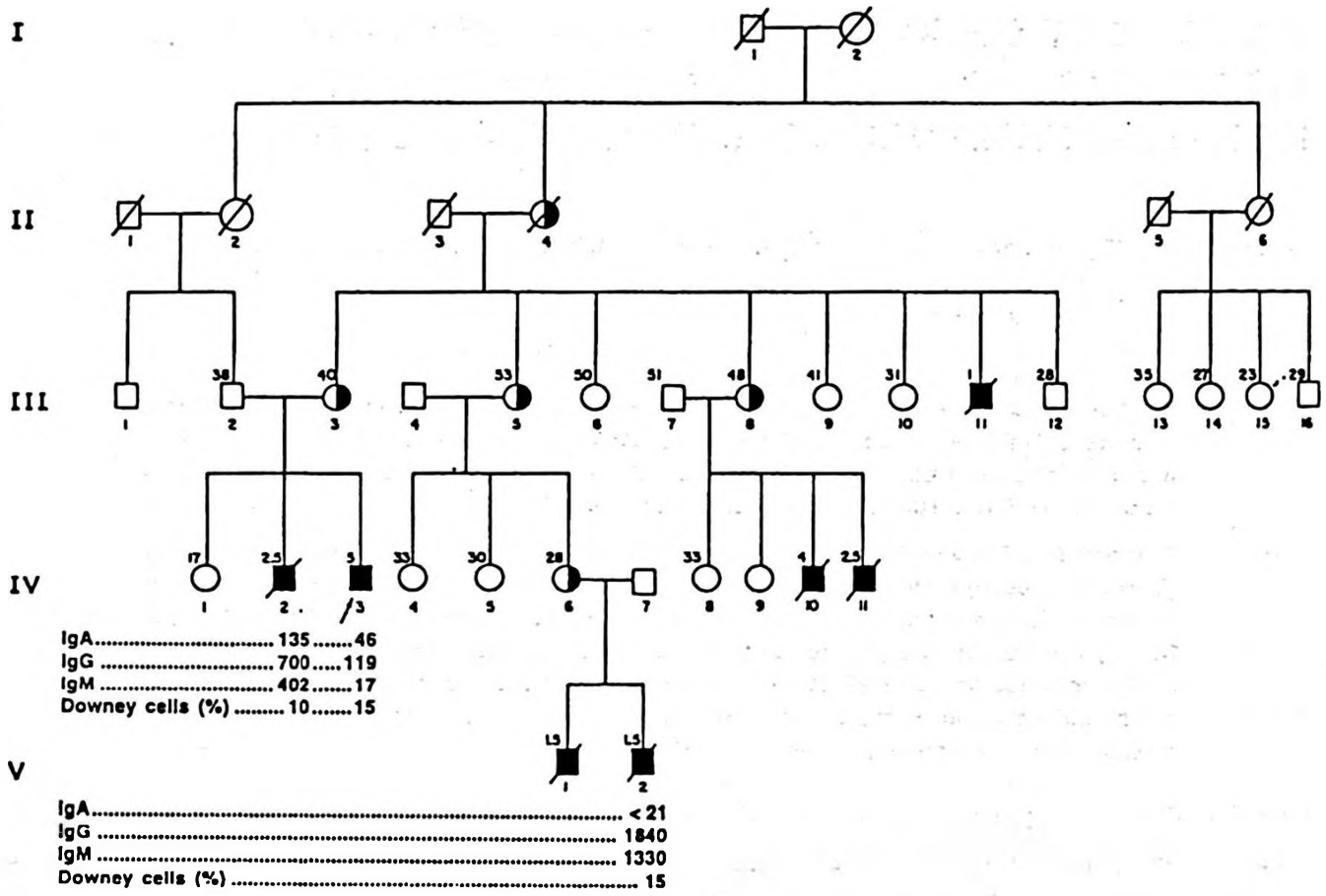

Fig. 1: Pedigree of the family.

On physical examination, he was an ill-looking boy with a body temperature of 39.5 °C He had hepatomegaly of 8 cm and splenomegaly of 10 cm below the respective costal margins.

On laboratory examination, the hemoglobin (Hb) level was 9.4 g/dL, white blood cell count (WBC) 4.600/mm^3 and the thrombocyte count was 220.000/mm^3. In the peripheral blood smear, 70 percent of the white cells were lymphocytes; Downey cells and normochrome normocytic erythrocytes were also noted. Liver function tests, viral and bacterial investigations for hepatitis B, C, cytomegalovirus (CMV), salmonella and brucella were negative. The patient also had hypoglobulinemia (IgG = 119 mg/dl, IgA = 46 mg/dl and IgM = 17 mg/dl).

Bone marrow aspiration was normal, and a splenic fine needle aspiration revealed hemophagocytosis.

The patient had a continuous high-grade fever and massive hepatosplenomegaly, and antibiotic treatment was ineffective. High-dose methylprednisolone (30 mg/kg/day for one week, 20 mg/kg/day for the second week, and 10 mg/kg/day for two weeks) treatment was started orally during the second week after admission, and the patient was without fever within 24 hours. In addition

to methylprednisolone, he was given intravenous (IV) VP-16 (150 mg/m^2) and intrathecal therapy with methotrexate (10 mg) and cytosine arabinoside (20 mg); prednisolone (10 mg) was given once a week for four weeks and intravenous gammaglobulin (400 mg/kg) monthly (Fig. 2). The Hb, hematocrit and WBC counts improved gradually, and the hepatosplenomegaly regressed within two months. Maintenance therapy consisted of progressively less frequent treatments with intravenous VP-16 down to one infusion of 150 mg/m^2 every sixth week, which was discontinued 15 months after the diagnosis. As of this writing, the patient was six years old, clinically healthy and receiving IV immunoglobulin monthly. The patient is considered to have XLP. Serum and DNA samples from family members were shipped to the University of Nebraska Medical Center (Dr. Purtilo) for analysis of XLP. Antibodies to EBV antigens [viral capsid antigen (VCA)-IgM < 10:10., IgG < 1:10., Epstein-Barr nuclear antigen (EBNA) < 1:5]. were lacking, consistent with XLP disease. The family was screened for eight markers on the X-chromosome, close to the XLP gene. The markers DXS-37 and DXS-10 have been identified as informative for detection of carrier females in the family.

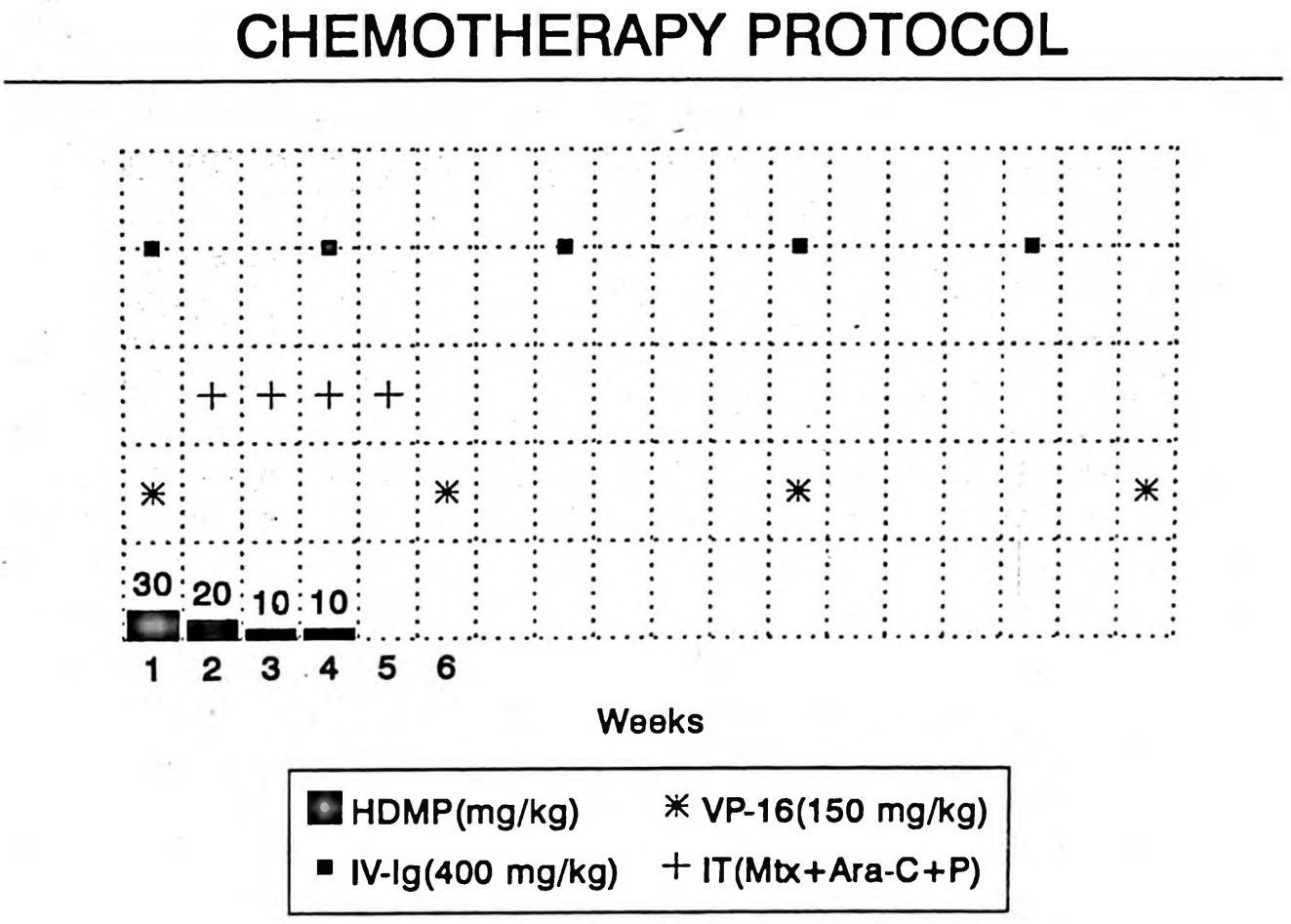

Fig. 2: The Chemotherapy Protocol. VP-16: Etoposide, i.v.: intravenous immunoglobulin, I.T.: Intratechal, Mtx: Methotrexate, ARA C: Cytosine Arabinoside, P: Prednisolone, HDMP: High-dose Methyl Prednisolone.

We also studied two other members of this family, in which seven boys were affected by XLP.

Case 2

In 1986, older brother of Case 1 (Fig. 1, IV-2) had a two-week febrile episode with massive hepatosplenomegaly and skin rashes at the age of 2.5 years. Laboratory data revealed hemoglobin 7.4 g/dL, WBC count 4,700/mm^3 (10% Downey cells), aspartate aminotransferase 305 I.U and alanine aminotransferase 155 I.U. The patient died within three months with profound lymphoid depletion as well as necrosis of the spleen and liver on autopsy.

Case 3

An 18-month-old boy (Fig. 1, V-2) was admitted to our hospital in 1994 with a two-week history of febrile episodes and massive hepatosplenomegaly. His elder brother had died of a similar condition at the age of 1.5 years. Laboratory data revealed Hb 7.3 g/dL, WBC 6,300/mm^3, platelet count 40,000/mm^3, aspartate aminotransferase 1013 IU, alanine transferase 302 IU and total bilirubin of 5.4 mg/dL. Viral and bacterial investigations for hepatitis A, B, C, CMV, toxoplasmosis, salmonella and brucella were negative. Bone marrow aspiration showed a lymphocyte predominance. The patient died of hepatic failure within 24 hours of admission. Postmortem examination revealed extensive necrosis of the liver.

Discussion

The immune defenses of the body normally react against an EBV infection by producing specific antibodies. In normal subjects, following EBV infection, B lymphocytes are transformed into proliferating lymphoblastoid cells. These cells can be killed by other proliferating cells induced by the immune response. EBV-induced lymphoproliferation is fatal in some subjects with both inherited and acquired immunodeficiencies.

Before EBV infection occurs, boys with an XLP mutation have normal cellular and humoral immune responses and respond normally to bacterial and viral infections other than EBV. Following EBV infection, about 75 percent of boys with XLP disease develop fatal IM, with liver destruction being the frequent cause of death[1-3]. In XLP, the inherited immunodeficiency is transmitted at the time of conception from unaffected women, known as carriers, to some of their male children.

Treatment of patients with XLP with antiviral agents such as acyclovir, interferon-gamma and interferon-alpha combined with high-dose immunoglobulins has been disappointing[4, 5].

In the treatment of our patient, high-dose methylprednisolone and VP-16 was used successfully. Similar therapy has also been used successfully in the treatment of some patients with hemophagocytic lymphohistiocytosis and Griscelli syndrome[6,7]. It is probable that glucocorticoid hormones inhibit the production of tumor necrosis factor, which is an inflammatory cytokine in the inflammatory response[6]. Good responses with high-dose methylprednisolone have been reported in hematologic disorders[8]. VP-16 has also been used successfully in the treatment of the acute phase of hemophagocytic lymphohistiocytosis syndromes. A boy with XLP and acute infectious mononucleosis reportedly underwent clinical remission with VP-16 and subsequent allogeneic bone morrow transplantation from a sibling[3]. Recently four boys with XLP received allogeneic bone marrow transplants, but only one of them is alive and well up to 24 months after transplantation[3]. Williams et al.[9] showed that allogeneic bone marrow transplantation can correct the lethal immune deficits in a patient with XLP and non-Hodgkin's lymphoma. Another child is alive and well more than one year after having received a transfusion of umbilical cord blood from his newborn brother[10]. Our patient is doing well four years after the diagnosis.

Note Added in Proof

Our personel communication with Dr. Gross revealed some unpublished long-term survivals according to their retrospective review of XLP registry cases.

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