A CASE OF HEMOPHILIA A ASSOCIATED WITH HODGKIN'S DISEASE*

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SUMMARY: Koç A, Varan A, Büyükpamukçu M, Gürgey A. (Hematology and Oncology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). A case of hemophilia A associated with Hodgkin's disease. Turk J Pediatr 1999; 41: 517-520.

Lymphoreticular malignancies are more common in patients with hemophilia, but it is usually attributed to human immunodeficiency virus (HIV) infection associated with repeated use of blood products. However, there are a couple of hemophiliac patients with malignancies but without HIV infection in the literature. We report a case of a hemophiliac patients who had Hodgkin's disease at 2.3 years old without any congenital or acquired immunodeficiency and without use of any blood products. This patient showed that malignancy can develop in hemophiliacs without HIV infection, but further studies are needed to clarify whether hemophiliacs are more susceptible to malignancies. *Key words: hemophilia, Hodgkin's disease, malignancy.*

The inherited immunodeficiency states such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, and some hematological disorders such as Fanconi's anemia are associated with a high incidence of malignancy[1,2]. Non-Hodgkin's lymphoma (NHL) is the most common malignant disease in patients with hemophilia, but it is usually attributed to human immunodeficiency virus (HIV) infection associated with repeated use of blood products[3,4]. Other malignancies in hemophiliacs are also reported, with or without HIV infection[5-7].

We report the case of 2.3-year-old hemophiliac child with Hodgkin's lymphoma without HIV infection.

Case Report

A 2.3-year-old by with hemophilia A was brought to İhsan Doğramacı Children's Hospital in June 1997 with left sub-auricular and upper cervical mass. When he was two years old, he was diagnosed as having hemophilia A, without any

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bleeding, because of his family history, which included three patients diagnosed with hemophilia A. The patient had no underlying predisposing factor for development of cancer. The laboratory tests revealed the following prothrombin time (PT) of 13 seconds and an activated partial thromboplastin time (aPTT) of 67 seconds. Bleeding time was normal. A thromboplastin generation test indicated that the boy had factor VIII deficiency (Factor VIII was 4% and Factor IX was 75%). He did not receive any blood product as he had no severe bleeding episodes.

Physical examination revealed a well developed but pale child. Massive cervical lymphadenopathy on the left side was noted. The liver was palpable 3 cm and the spleen 4 cm below the respective costal margins. The hemoglobin level was 7.8 g/dl, leukocyte count 8,000/mm^3 with 53 percent neutrophils, 36 percent lymphocytes, 8 percent monocytes and 2 percent eosinophils. Bone marrow aspiration was normal. In immunological and viral studies, HIV was negative, anti CMV IgG>250 IU/ml, IgM (+); anti rubella IgG (–), IgM (–); anti toxoplasma IgG (–), IgM (–); nitroblue tetrazolium test (NBT): 100%, quantitative immunoglobulins: IgG 1600 mg/dl (N 604-1941), IGM 271 mg/dl (N 71-235), IgA 369 mg/dl (N 26-296); PPD (–). Computerized tomographic (CT) examination of the cervical region showed left cervical necrotic mass through to superior mediastinum and thoracal CT showed upper mediastinal mass. Abdominal CT was normal. Mass biopsy was performed, and Hodgkin's disease (HD) with lymphocyte depletion was diagnosed.

He had been treated with adriamycin (25 mg/m^3), bleomycin (10 mg/m^3), vinblastine (6 mg/m^2), and dacarbazine (375 mg/m^2) (ABVD protocol). After initial treatment, he did not respond to his therapy during the following three months, and in October 1997 his treatment was changed to the ABVD-COPP (cyclophosphamide, oncovin, procarbazine, prednisone) alternate treatment protocol. Radiotherapy was given in December 1997. In January 1998, six months after he started chemotherapy, his lymphoma relapsed. He did not respond to therapy and died two weeks after the relapse, in February 1998, because of overwhelming infections.

Discussion

Children with inherited and acquired immunodeficiency syndromes and those with iatrogenically induced immunodeficiency have a much higher risk of developing lymphoreticular malignancies than expected[3,4,8,9]. Since HIV infection leads no progressive loss of cellular immunity, it is probable that these malignancies result from the progressive reactivation or loss of immunologic control of latent oncogenic viruses[4,10]. NHL in particular was found to be more frequent in a hemophiliac who had been infected with HIV[3,4]. The mean CD 4

at presentation of NHL was extremely low in NHL associated with HIV infection in hemophiliac patients[3]. It is possible that the CD 4 number in hemophiliac patients at NHL presentation reflects not only the result of underlying HIV infection with a quantitative decrease in CD 4, but is also related to chronic foreign protein and antigenic exposure with chronic blood transfusions[3,11-15]. There are several reports of diminished helper/suppressor T lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions without HIV infection[4,11-15].

Lymphomas and other malignancies have also been reported in hemophiliac patients without HIV infection. Ragni et al.[3] reported three NHL cases in hemophiliacs without HIV infection, two of them with mild hemophilia, one treated only with cryoprecipitate and one who had never been treated with blood products. Bouhasin et al.[7] and Green et al.[6] reported acute leukemia in patients with hemophilia. Altay et al.[5] reported two acute leukemia cases with mild hemophilia from our clinics previously. One of them had acute lymphoblastic leukemia at the age of 10 years, and he had only one blood transfusion and one fresh frozen plasma before leukemia was diagnosed. The other had acute myelomonocytic leukemia at the age of 1.5 years and the had had only two plasma infusions. Levine et al.[16] reported familial nasopharyngeal carcinoma cases also with hemophilia.

Our patient had clinically mild hemophilia and had not received any blood products before HD was diagnosed. He did not have HIV infection or other congenital or acquired immunodeficiency states.

Hodgkin's disease is rarely diagnosed in children younger than five years[8]. Most cases of HD associated with HIV infection have a pathologically high stage and bone marrow involvement with the initial diagnosis, and are histologically subclassified as mixed cellularity and nodular sclerosis[9,17-19], contrary to the cases of our patients.

In conclusion, malignancy can develop in hemophiliacs without HIV infection. It is also possible that the association of Hodgkin's disease in our patient was coincidental. However, further studies are needed to clarify whether hemophiliacs are more susceptiple to malignancies.

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