Acute lymphoblastic leukemia in a child with Wilson disease

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Wilson disease is an autosomal recessively inherited disease of copper metabolism and is characterized by liver and central nervous system dysfunction. The heterozygote carrier state rate is about one in 90 persons and the incidence of the disease is about 30 in 1,000,000. Although leukemia is the most common form of childhood malignancies, the probability of the presence of Wilson disease and acute lymphoblastic leukemia in the same patient is very low. We report an unusual case of a child with Wilson disease who developed acute lymphoblastic leukemia in three months.

Key words: Wilson disease, acute lymphoblastic leukemia.

Wilson disease (WD) is a rare inherited disease of copper metabolism, characterized by liver and central nervous system dysfunction[1]. It is transmitted through a recessive gene located on chromosome 13[2]. The heterozygote carrier state rate is about one in 90 persons and the incidence of the disease is about 30 in 1,000,000[1]. In certain countries, including Turkey, in which the number of consanguineous marriages is high, this rate may be higher than the estimation[3].

Leukemia is the most common form of childhood malignancies, and its incidence in white children younger than 15 years of age is approximately 31 per million per year[4]. The most common form of leukemia in childhood is acute lymphoblastic leukemia (ALL). The mortality rate is still high and it is inevitably fatal without treatment.

We report an unusual case of a child with WD having ALL. To our best knowledge, this is the first report of WD associated with ALL.

Case Report

A 12-year-old boy presented with walking and speech disorders. His parents were first-degree cousins. His physical examination showed ataxia and dysarthria. He had no hepatosplenomegaly. Kayser-Fleischer rings were positive on ophthalmologic examination. Liver function tests were normal and serum ceruloplasmin level was undetectable. Daily urinary copper excretion was 840 μg (normal <40 μg). He was diagnosed as WD with neurologic presentation. D-penicillamine, zinc sulfate and a low copper diet were started.

Three months after the diagnosis of WD, he was admitted to the hospital with the complaints of fever, pallor, fatigue, and night sweating. His body temperature was 38.2°C. On physical examination he was pale, had mask face, and bruises on extremities. Liver and spleen were palpable four and three cm below the right and left costal margins, respectively. His speech showed marked dysarthria.

Hematological studies showed anemia (hemoglobin level 8.2 g/dl), thrombocytopenia (platelet count 49,000/mm^3), and leukocytosis (white blood cell count 161,000/mm^3). All leukocytes were blasts on peripheral blood smear and bone marrow aspiration revealed that 95 percent of cells were CALLA positive B cell immunophenotype lymphoblasts. Alanine aminotransferase level was 62 IU/L, aspartate aminotransferase 54 IU/L, and total protein and albumin levels were normal. Serology of hepatitis A, B, C, cytomegalovirus, and Epstein-Barr virus were found negative. Abdominal ultrasonography showed hepatosplenomegaly and heterogeneity of the liver. Liver biopsy could not be performed due to severe thrombocytopenia. St. Jude total therapy study XI protocol was started[5]. Liver and spleen became smaller during chemotherapy. He

developed neutropenic sepsis during treatment and his clinical situation deteriorated. The parents insisted on discharging him, and he died at home.

Discusison

Most patients with WD present during childhood and the majority have hepatic presentation. Other presenting features are neuropsychiatric, hematological, endocrinologic, and renal abnormalities[1]. Although the diagnosis of WD may be problematic in some patients, in our case, the presence of a very low serum ceruloplasmin level, increased daily urinary copper excretion, and Kayser-Fleischer rings confirmed the diagnosis. ALL developed in three months and worsened his situation.

Although ALL is primarily a disease of bone marrow, any organ or tissue such as liver and spleen may be infiltrated by abnormal cells. On initial examination, most patients with ALL are likely to have pancytopenia[6]; anemia and thrombocytopenia were due to ALL in our patient. In fact, various factors may be responsible for anemia and thrombocytopenia in a patient with WD. Penicillamine therapy may cause pancytopenia. The other possibility is the presence of asymptomatic cirrhosis at the time of diagnosis, and the development of hypersplenism. Although a significant proportion of patients with ALL have leukocyte counts less than 3,000/mm^3, one-fifth of them have leukocytosis as in our patient[6]. Our patient had leukocytosis, and lymphoblasts were easily recognized on peripheral blood smear examination. Thus, the diagnosis of ALL was promptly established.

Wilson disease has been mapped to chromosome 13q14.3, and it has been shown recently that it encodes a copper transporting P-type ATPase[7,8]. Several chromosomal abnormalities, including hyperdiploidy, hypodiploidy, translocations, and deletions, have been shown in ALL, and they can help define the subtypes of leukemia[6]. Chromosomal deletion on chromosome 13 has been reported in patients with T-lineage ALL[9]. But, frequent deletions of the 13q14.3 region (D13S19), a tumor-suppressor gene, have been shown in patients with B-cell chronic lymphocytic leukemia[10]. The probability of the presence of WD and ALL in the same patient is very low. Even if we consider that all WD patients present during childhood, the presence of both diseases in one patient by coincidence is low. It is hard to speculate that there is an association between the two disease. It would be interesting if we could evaluate the DNA of our patient with B-cell ALL both WD mutations and D13S319 mutations.

The pyossibility of leukemia should be kept in mind in patients with WD in whom hepatosplenomegaly and pancytopenia developed or progressed within a short time. It may present a diagnostic challenge for the physician if the patient presents with pancytopenia but without abnormal cells on peripheral blood smear. In our case, because the patient had leukocytosis instead of leukopenia and blasts on his peripheral blood smear, we could make the diagnosis of ALL without delay.

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