Two Cases of Primary Biliary Cirrhosis Complicated by Acute Leukemia

Hironobu Saito, Kyoko Monoe, Yukiko Kanno, Atsushi Takahashi, Tsuyoshi Rai, Atsushi Irisawa and Hiromasa Ohira

Abstract

Case 1 was a 43-year-old woman, who was diagnosed as having PBC. After one month, she was hospitalized owing to sudden temporary unconsciousness. She was diagnosed as having acute lymphoid leukemia (ALL) by bone marrow examination. Chemotherapy was done, but she died after 6 months. Case 2 was a 54-year-old woman, who was diagnosed as having PBC with CREST syndrome. Seven years later, she was diagnosed as having acute promyelocytic leukemia (APL) by bone marrow examination. Chemotherapy was continued, and her symptoms are at present, stable. To date, there have been no reports of PBC complicated by acute leukemia.

Key words: primary biliary cirrhosis, acute lymphoid leukemia, acute promyelocytic leukemia

(DOI: 10.2169/internalmedicine.46.6037)

Introduction

Primary biliary cirrhosis (PBC) is characterized by abnormalities in both cellular and humoral immunity. It is associated with diseases which are presumably autoimmune, such as Sjogren’s syndrome, rheumatoid arthritis, and scleroderma. Some hepatic and extrahepatic malignancies are reported as complications of PBC; however, malignant blood dyscrasia is a very rare complication of PBC. Here, we describe two cases of PBC complicated by acute leukemia.

Case Report

Case 1. A 43-year-old woman presented to our department in 1997 because liver dysfunction was detected by mass screening. Her mother had been diagnosed with PBC at the age of 58 years. She had no history of alcohol abuse or drug allergy. The results of the physical examination were normal and there was no sign of portal hypertension. Laboratory data showed an elevated level of alkaline phosphatase (ALP) (414 IU/L; normal, 125-335 IU/L) however, the other liver function test results and IgM level were normal. The titer of antinuclear antibodies (ANA) was 1 : 2560 and its pattern was centromere. Antimitochondrial antibodies (AMA) and AMA-M2 were negative, but Western-blot analysis of PDC-E2 (IgG class) was positive (Fig. 1). Antibodies to SS-A and SS-B were not examined. Results of hepatitis B and C serologic tests were negative. She was diagnosed as having PBC, although unfortunately a liver biopsy was not performed, and she was treated with ursodeoxycholic acid (UDCA). After one month, she was hospitalized owing to sudden temporary unconsciousness due to severe anemia. Examination of the blood showed anemia with a hemoglobin value of 6.3 g/dL, a red blood cell count of 222×10^6/mm^3, and a low platelet count of 0.6×10^9/mm^3. Laboratory data showed elevated levels of LDH (515 IU/L; normal, 275-475 IU/L). Surface markers of B-cell lymphocyte were positive (CD10 and CD19). The result of chromosomal analysis was t (9 ; 22). She was diagnosed as having acute lymphoid leukemia (ALL) by bone marrow examination. Chemotherapy by combination of adriamycin (ADM) + vincristine (VCR) + cyclophosphamide (CPM) + prednisolone (PSL) was planned, but her family did not approve. VCR+PSL therapy was performed and she died after 6 months.

Case 2. A 54-year-old woman was referred to our department in 1997 because of liver dysfunction and esophageal varices. She had suffered from Raynaud’s phenomenon for 2
years. She had no history of alcohol abuse or drug allergy. Physical examination showed telangiectasia on her lip and splenomegaly but there was no symptom of itching. Laboratory data showed elevated levels of ALP (502 IU/L), gamma-glutamyl transpeptidase (GGT) (228 IU/L; normal, 6-30 IU/L) and IgM (448 mg/dL; normal, 52-270 mg/dL). The titer of ANA was 1:10240 and its pattern was centromere. The titer of AMA was 1: 40 and the index of AMA-M2 antibody was 65 (normal, <0.7). Antibodies to SS-A and SS-B were negative. The results of hepatitis B and C serologic tests were negative. Histological analysis of the liver biopsy specimen revealed findings of chronic non-suppurative destructive cholangitis (CNSDC) (Fig. 2). She was diagnosed as having PBC with incomplete CREST syndrome and treated with UDCA. In August 2004, she was hospitalized due to high fever. Examination of the blood showed a low white blood cell count of 500/mm³, and anemia with a hemoglobin value of 7.7 g/dL, a red blood cell count of 206×10³/mm³, and a low platelet count of 12×10³/mm³. Laboratory data showed elevated levels of UA (7.7 mg/dL; normal, 2.6-6.0 IU/L), and FDP (74.2 μg/mL; normal, 0-5 μg/mL). Surface makers of leukemic cells were positive (CD13 and CD33). The result of chromosomal analysis was t (15 ; 17). She was diagnosed as having acute promyelocytic leukemia (APL) by bone marrow examination. Chemotherapy by all-trans retinoic acid (ATRA) + cytarabine (AraC) + idarubicin hydrochloride (IDR) has been continued for APL, and her symptoms are at present, stable.

Discussion

Malignant blood dyscrasia complicating PBC, in particular the lymphoproliferative neoplasm, has been reported (1, 2). However, the incidence of this disease is not specifically high in patients with PBC. The pathogenesis of lymphoma or multiple myeloma complicating PBC has been suggested with autoimmune mechanisms (3). It is difficult to explain the pathogenesis of the association with ALL or APL and PBC by an autoimmune mechanism. Autoantibodies against Sp100 and promyelocytic leukemia protein (PML), which are aberrantly expressed in promyelocytic leukemia cells (4), are found simultaneously in 90% of the patients with PBC. The Sp100 and PML are present in the so-called nuclear dots and against the autoantibodies which are present in a subpopulation of PBC patients (5). However, these antibodies were negative in case 2.

Recent reports have indicated that patients with PBC may have a higher incidence of hepatobiliary malignancies (6, 7). Some data suggest that there is an increased risk of breast cancer in PBC (8). On the other hand, PBC is associated with autoimmune diseases such as Sjögren’s syndrome, rheumatoid arthritis, and scleroderma. Sjögren’s syndrome and scleroderma have been noted to have an increased frequency of malignancy. Some reports have shown acute leukemia in these diseases (9-12), however the overall frequency of hematologic malignancy in patients with scleroderma is in fact lower than the nationwide frequency (12). In the present case 1 it was not complicated by Sjögren’s syndrome or scleroderma, but case 2 was complicated by CREST syndrome, which is a limited type of scleroderma. Therefore, acute leukemia may be associated with autoimmune diseases complicated by PBC, as in case 2.

The occurrence of acute leukemia in patients receiving
Chemotherapeutic agents for inflammatory and connective tissue diseases has been reported (13). These agents may be related to the development of second neoplasms. The present cases were never treated with chemotherapeutic agents and they were treated with UDCA. Although the immunosuppressive effects of ursodeoxycholic acid have been observed in an in vitro study on human peripheral blood mononuclear cells (14), there is no report on the development of a second neoplasm. Adversely, UDCA is thought to be chemopreventive for colorectal cancer (15). Thus, it is difficult to relate the pathogenesis of acute leukemia to UDCA.

Since there have been no reports of PBC complicated by acute leukemia, the present cases may have been accidental events. However, to clarify the association of PBC and acute leukemia, further study of similar cases is needed.

References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html