Primary Biliary Cirrhosis Following Chemotherapy for Hodgkin’s Lymphoma

Kentaro Yoneda, Kazushi Sugimoto, Katsuya Shiraki, Junichiro Tanaka, Tetsuya Beppu, Hiroyuki Fuke, Norihiko Yamamoto and Yoshiyuki Takei

Abstract

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease primarily affecting middle-aged women. Although little is known about the etiology of PBC, it may be induced by an autoimmune response. Here, we describe a rare case of appearance of PBC following chemotherapy for Hodgkin’s lymphoma.

Key words: Primary biliary cirrhosis, lymphoma

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Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease primarily affecting middle-aged women; it is an autoimmune liver disease (1). The cause of PBC is unknown, but is thought to be the result of immunoregulation leading to progressive destruction of interlobular bile ducts and selective disturbance of bile secretion (1, 2). The trigger event is typically unknown, but PBC can be induced by drugs, environment and/or infections agents (1, 3, 4). However, PBC induced by chemotherapeutic drugs has not been reported. Here, we report a case of PBC following the use of chemotherapeutic drugs for Hodgkin’s lymphoma.

Case Report

A 64-year-old man presented with a mass in his left arm-pit with extended skin eruption from his chest to his back. He was admitted to the Hematology Department of our hospital because the excised biopsy specimen confirmed Hodgkin’s lymphoma. He underwent ABVD chemotherapy (Adriamycin, bleomycin, vinblastine, dacarbazine) for 8 cycles, and radiation therapy was performed. Hodgkin’s lymphoma responded to this regimen, and the patient exhibited complete remission.

Two months after receiving chemotherapy and radiation therapy for Hodgkin’s lymphoma, he was admitted to our department for liver dysfunction and prolonged cholestasis. He did not complain of fatigue or loss of body weight. Physical examination revealed no hepatomegaly, no ascites and no masses. Laboratory data showed alkaline phosphatase (ALP) levels of 870 IU/L (normal, 104-338), gamma glutamyltransferase levels of 761 IU/L (normal, 12-50), aspartate aminotransferase (AST) of 127 IU/L (normal, 10-27), alanine aminotransferase (ALT) of 155 IU/L (normal, 5-37), total bilirubin of 0.7g/dL (normal, 0.3-1.2), elevated IgM levels [340 ng/dL (normal, 40-194) ] and total cholesterol levels of 233 mg/dL (normal, 160-219). Hepatitis profile for hepatitis B and C was negative. Anti-mitochondrial antibody titer (AMA) was 640-fold beyond the normal upper limit, and antinuclear antibody was 20-fold.

Abdominal ultrasound revealed a slightly atrophic liver with dull edge, while computed tomography (CT) and magnetic resonance imaging (MRI) revealed a normal bile duct. Liver biopsy showed inflammatory destruction of the intrahepatic septal and interlobular bile ducts within the portal space, and expanded portal tracts by lymphocytes comprising sparse neutrophils or eosinophils, thus suggesting PBC (Scheuer stage I) (Fig. 1).

Histological and pathological findings showed that plasma cells and inflammatory cells had infiltrated beyond the basement membrane, and proliferation of bile ducts was observed. A diagnosis of PBC was confirmed based on cholestasis, positive AMA and histological findings. The patient...
was started on ursodeoxycholic acid (UDCA) at 600 mg three times daily, and standard liver function tests, including AST, ALT, ALP and IgM returned to normal after several months. In contrast, AMA returned to normal (less than 20-fold) when one year passed. Liver biopsy was not done.

**Discussion**

PBC is a chronic cholestatic, autoimmune liver disease, the cause of which is unknown (1, 2). Middle-aged women typically suffer from this disease, and immunological and genetic factors (familial association with HLA-DR8 locus) are known to play a role in onset (1). PBC exhibits elevated serum IgM and serum hyper autoantibodies, while liver biopsy specimens reveal reactions with antigens on the surface of biliary epithelial cells (1-3).

Some drugs induce liver injury via an autoimmune mechanism (4). Metabolites derived from drugs may cause an autoimmune response or lead to direct toxic effects in hepatocytes. In addition, chemotherapeutic drugs, Chinese herbs (5) and the use of interferon therapy (6) have been reported to induce autoimmune hepatitis.

Drugs (phenothiazine, methyltestosterone, tolbutamide, interferon) (7, 8), environment and/or infectious agents can trigger PBC. However, there have been no reports of PBC appearing after the use of chemotherapy. Furthermore, drug-induced PBC following the administration of medication is very rare.

In this case, before the use of chemotherapeutic drugs, laboratory data of this case was in the normal range including liver function tests and IgM (AMA was not measured). And then after chemotherapy, this patient developed PBC as noted on his laboratory data and liver biopsy specimen; after UDCA administration IgM and AMA were within the normal range. Thus, PBC onset may have occurred due to autoimmune activity following immunosuppression.

Several studies have reported that PBC may be accompanied by lymphoma, but the present patient developed PBC after the remission of lymphoma. Therefore, lymphoma itself may not have been related to PBC.

In summary, we report a rare case of PBC in a male patient after undergoing chemotherapy. Autoimmune activity should thus be closely monitored after chemotherapy, and PBC should be considered if liver dysfunction is observed.

**References**