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Case Report

Resolution of Chronic Hepatitis B-Associated Autoimmune Neutropenia With Interferon-α Therapy

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Chronic hepatitis B virus (HBV) is one of the most prevalent viral infections, affecting at least 1 million people in the United States and 300 million people worldwide (1). Although cirrhosis and hepatocellular carcinoma are the most important complications of chronic HBV infection, extrahepatic manifestations also occur, including immune-mediated diseases such as polyarteritis nodosa (2), cryoglobulinemia (3), and membranous glomerulopathy (4). Although uncommon, these extrahepatic manifestations can cause significant morbidity and mortality. The recognition of these HBV complications is important because management of the underlying viral infection may result in resolution of the extrahepatic manifestations.

We report a case of autoimmune neutropenia associated with chronic HBV and its response to interferon-α (IFN-α) therapy.

CASE REPORT

The patient was a Korean-born child who was adopted when aged 5 months by US parents. Her serum test results at 11 months were positive for hepatitis B surface antigen (HBsAg). There was no information on the status of her biologic parents, but her adoptive parents' test results were negative for HBsAg and antibody (anti-HBs). She was referred to the Clinical Center of the National Institutes of Health (NIH) for evaluation and treatment when aged 15 months.

When first examined, she had no history of jaundice, dark urine, bruising, abdominal swelling, gastrointestinal bleeding, severe infections, or allergies. An atrial septal defect was diagnosed shortly after birth, but subsequent echocardiography showed spontaneous closure of the foramen ovale. She had had no invasive procedures and had not received blood transfusions. Physical findings were normal: neither the liver nor spleen was enlarged, nor were there other signs of chronic liver disease. Serum testing results were positive for HBsAg and hepatitis B e antigen (HBeAg) and negative for anti-HBs and antibody to HBeAg (anti-HBe). Serum HBV DNA level was 3,197 million genome equivalents/mL (Meq) using the branched DNA signal amplification assay (Bayer Diagnostics, Emeryville, CA). Antibodies to hepatitis A, C, and D were negative, as was the antibody to human immunodeficiency virus. Serum alanine aminotransferase (ALT) was 125 IU/L (normal, <41), and aspartate aminotransferase (AST) was 135 IU/L (normal, <34). Serum alkaline phosphatase (164 IU/mL), γ-glutamyl transpeptidase (30 IU/L), total bilirubin (0.3 mg/dL), albumin (4.5 g/dL), prothrombin time (11.7 seconds), and α-fetoprotein (1.1 ng/mL) were all within normal ranges. She also had normal ceruloplasmin (410 mg/L) and α1-antitrypsin (170 mg/dL) levels and normal iron saturation (16%). Her total leukocyte count was normal (4,700 cells/mm^3), but she had persistently low absolute neutrophil counts, ranging from 188 to 387 cells/mm^3 on many determinations. Hemoglobin was 11.9 g/dL, and platelet count was 457,000/mm^3. Antinuclear antibodies were negative, but low levels of antineutrophil antibodies were present. A bone marrow aspirate showed a normocellular marrow with normal megakaryocyte, erythroid, and myeloid series and normal myeloid differentiation. A percutaneous liver biopsy showed moderate chronic portal inflammatory infiltrates associated with mild focal periportal and lobular necrosis, but no fibrosis was seen. The histology activity index was scored as 1 for periportal necrosis and inflammation, 3 for lobular necrosis and inflammation, 1 for portal inflammation, and 0 for fibrosis (5). Immunohistochemical stains for hepatic HBsAg and hepatitis B core antigen were positive.

She was monitored with no specific therapy for 2 years. Serum ALT and AST remained elevated, and neutrophil counts were generally less than 400 cells/mm^3

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except for one occasion when they were 2,448 cells/mm^3. When the patient was aged 3 years, antiviral therapy was considered. After thorough discussions with the parents about risks and benefits of therapy and signed informed consent was obtained, IFN-α_{2b} was started in a dose of 1.7 MU (3 MU/m^2) subcutaneously three times for the first week, followed by 3.4 MU (6 MU/m^2) thrice weekly for the following 23 weeks (6). She tolerated therapy well without requiring dose modification or interruption. During the first month of treatment, HBV DNA levels decreased from 1,489 to 155 Meq/mL, and neutrophils increased from 232 to 880 cells/mm^3 (Fig. 1). HBV DNA levels decreased below the limit of detection of the assay (<0.7 Meq/mL) by the end of therapy, and neutrophil counts increased to the normal range. One year after ending therapy, serum HBeAg and HBsAg were no longer detectable, and she had developed anti-HBe and anti-HBs. Antineutrophil antibodies were retested and found to be negative after treatment. During the subsequent 3 years of follow-up evaluation, serum ALT and AST levels remained normal, and neutrophil counts ranged from 1,520 to 2,651 cells/mm^3. The patient remained asymptomatic of liver disease and had no significant bacterial infections.

DISCUSSION

Neutropenia can accompany viral hepatitis due to several causes. The most common cause is hypersplenism resulting from cirrhosis and portal hypertension. The neutropenia of cirrhosis often complicates therapy with IFN-α because this cytokine has dose-related myelosuppressive activity that decreases neutrophil counts by 30% to 50%. In patients with preexisting neutropenia, neutrophil counts may decrease to fewer than 500 cells/mm^3 during therapy and lead to dose modification or early discontinuation of therapy.

More rarely, neutropenia can be a complication of hepatitis in the absence of cirrhosis. This complication occurs usually in patients with acute viral hepatitis. Thus, there is a well-documented association between severe acute hepatitis of unknown cause (presumably a non–A-E hepatitis virus) and pancytopenia (aplastic anemia) (7). Typically, this syndrome presents acutely and has a high mortality rate unless there is prompt treatment with immunosuppressive agents, such as antithymocyte globulin and cyclosporine, or bone marrow transplantation. Although this syndrome is generally believed to be caused by infection with a hepatitis virus, it may actually be autoimmune in nature. This possibility is supported by the prompt clinical response to immunosuppressive management and also by in vitro studies showing that peripheral blood and marrow cells and their supernatants from affected patients can suppress hematopoiesis by autologous and normal marrow (8).

Rarely, isolated neutropenia without changes in erythrocyte or platelet counts has been associated with acute hepatitis. In contrast to our case, the few published reports have been associated with a hypocellular bone marrow or maturational arrest of the myeloid series (9–12). HBV has been implicated in two cases of hepatitis-

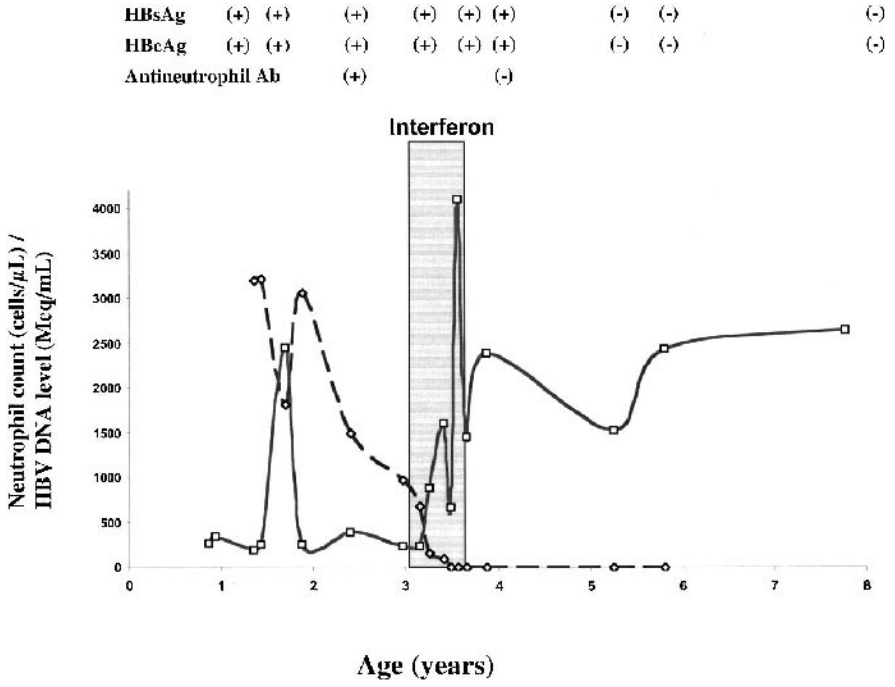

FIG. 1. Absolute neutrophil counts (continuous line) and results of HBV DNA (dashed line) testing in a child with chronic hepatitis B virus and autoimmune neutropenia who was successfully treated with a 6-month course of interferon-α and ultimately had complete resolution of hepatitis B virus and neutropenia. HBeAg, HBsAg, and antineutrophil antibodies are expressed as positive (+) or negative (–) at the respective time points.

related neutropenia, and in both, the hematologic abnormality was transient and self-limited and occurred after an acute infection.

Autoimmune neutropenia, also known as chronic benign neutropenia of infancy and childhood, is a common cause of neutropenia in children and infants (13). This syndrome, however, has not been linked to chronic HBV. Autoimmune neutropenia can be successfully managed with colony-stimulating factors and often resolves spontaneously during the first years of life. At least one case of hepatitis-associated autoimmune neutropenia has been reported (14), but the patient's results reportedly were negative for HBsAg.

For the patient reported here, treatment with IFN-α led to a prompt decrease in HBV DNA levels followed by a decrease of serum aminotransferase levels to a normal range and eventually to loss of HBeAg and HBsAg. The virologic response was also accompanied by a dramatic increase of neutrophil counts to a normal range. It is possible that neutropenia and HBV were unrelated and that the autoimmune neutropenia resolved spontaneously, not as a direct result of antiviral therapy or clearance of HBV. However, the increase in neutrophil count during interferon therapy and the reversal of neutropenia concurrent with the decrease in HBV DNA levels, well before loss of HBsAg and HBeAg, suggest that the neutropenia was the direct effect of HBV. The mechanism by which HBV may induce neutropenia is not clear. HBV is believed to replicate in bone marrow cells and particularly leukocytes, but bone marrow examination in this patient showed normal numbers and maturation of the myeloid series. Thus, the neutropenia was more likely the result of peripheral sequestration or peripheral destruction of cells (as might be caused by antineutrophil antibodies) rather than direct bone marrow suppression.

Interferon-α therapy was given to this patient with considerable caution and concern. IFN-α is known to suppress bone marrow production of neutrophils, and a 30% to 50% decrease in neutrophil counts is typical during therapy (15,16). Thus, there was concern that neutropenia would worsen acutely during treatment and predispose the patient to severe bacterial infection. In addition, IFN-α therapy has been linked to the induction of autoimmune conditions such as thyroiditis (17), thrombocytopenia (18), type 2 diabetes (19), and myasthenia gravis (20). Therefore, there was additional concern that interferon would lead to worsening of the autoimmune neutropenia. In actuality, interferon treatment led to improvement in absolute neutrophil counts and eventual complete remission. These findings indicate that autoimmune neutropenia associated with chronic HBV should not be a contraindication to the use of IFN-α.

In conclusion, a child with chronic HBV and autoimmune neutropenia was successfully treated with IFN-α without worsening of neutropenia during treatment and with ultimate resolution of HBV and neutropenia.

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