Development of Pseudolymphoma of Liver Following Interferon-alpha Therapy for Chronic Hepatitis B

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A 42-year-old woman with biopsy-proven chronic hepatitis B, who had been treated with human leukocyte-derived interferon-alpha (huLe-IFNα) therapy for two months was found to have liver tumors on routine abdominal ultrasonography examination. She underwent laparotomy, and partial hepatectomy was performed under the clinical diagnosis of hepatocellular carcinoma. The lesions were diagnosed histologically as pseudolymphoma based on the massive infiltration of small mature lymphocytes and the presence of hyperplastic lymph follicles with germinal centers. Immunohistochemistry revealed polyclonal origin of the involved lymphocytes. The possible association between IFNα treatment and chronic hepatitis B with the development of pseudolymphoma is discussed.

(Key words: pseudolymphoma, liver, chronic hepatitis B, Interferon-alpha)

Introduction

Interferon-alpha (IFNα) preparations are increasingly used in the treatment of chronic hepatitis B and C due to its promising therapeutic effect (1, 2). However, IFNα has many side effects which can be a major impediment to its use (3). Although IFN has various effects on the immune system (4–8), which may be associated with the etiology of autoimmune diseases induced by IFNα (3), there has been no reports on the development of lymphoproliferative disorders following IFNα administration.

We report here the development of pseudolymphoma of the liver in a patient with chronic hepatitis B who had been treated by human leukocyte-derived interferon-alpha (huLe-IFNα) for two months.

Case Report

A 42-year-old female who is a hepatitis B virus (HBV) carrier had been followed up regularly by abdominal ultrasonography (US) or computerized tomography (CT) scan. Her serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) had risen to approximately 200 IU since January 1992, and her HBV-DNA polymerase (HBV-DNAp) had become positive (43 cpm) in March 1992. No mass lesions had been detected until April 1992 by both CT and US. She was diagnosed as having chronic active hepatitis B by ultrasonically guided fine-needle-aspiration liver biopsy performed on April 3, 1992. Her serum was positive for hepatitis B surface antigen (HBsAg), antibodies to hepatitis B e antigen (anti-HBe), and antibodies to hepatitis B core antigen (anti-HBc), but negative for antibodies to HBsAg (anti-HBs), HBeAg, antibodies to hepatitis C virus (anti-HCV) and antibodies to human immunodeficiency virus (anti-HIV). Her mother and a younger sister were also positive for HBsAg. She had never received blood transfusion and there was no past history of alcohol abuse or autoimmune disease. HuLe-IFNα (Sumiferon, Sumitomo Pharmaceutical Co., Ltd., Osaka) treatment at a dose of 6x10^6 I.U. per body three times per week was started on April 21, 1992. She had received a total of 28 treatments of huLe-IFNα treatment by June 22, 1992, and her liver function tests became normal. The routine abdominal US examination revealed two hypoechogenic lesions in the liver on July 27, 1992; one measured 1.6 cm in diameter in segment six (S6) and the other 1.1 cm in diameter in segment three (S3). She was referred to the Division of Hematology-Oncology, *the Department of Surgery and **Radiology, National Cancer Center Hospital, Chiba, ***the Pathology Division, National Cancer Center Hospital, Tokyo, ****the Department of Internal Medicine and *****Pathology, Nishinomiya Municipal Central Hospital, Hyogo.

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National Cancer Center Hospital East for further evaluation on September 16. She was well and asymptomatic. Liver and spleen were not palpable. There was no superficial lymphadenopathy. At the time of referral, her liver function tests and serum HBV-DNA were normal. Alpha-fetoprotein and proteins induced by vitamin K absence (PIVKA)-II were also within normal range. Abdominal US showed a hypoechoic mass in S6 and an isoechoic mass with hypoechoic rim in S3 of the liver, but the spleen did not show significant pathologic change and para-aortic lymph nodes were undetectable. The plain CT of the liver showed two low density areas; one 1.4 cm in diameter in S6 and the other 1.5 cm in diameter in S3, both of which appeared isodense on contrast-enhanced CT. The hepatic angiography demonstrated one distinct tumor stain in S6 (Fig. 1) and a faint stain in S3. The CT with arterial portography (CTAP) (9) presented a portal flow defect in S6 (Fig. 2) and several other small portal flow defects in the left lobe. She underwent laparotomy under the clinical diagnosis of hepatocellular carcinoma on October 12, 1992. At surgery, six small gray white nodules were seen on the surface of the liver in addition to two intrahepatic tumors which were detected by intraoperative US. The rest of the liver looked normal. The hepatohilar lymph nodes were not enlarged. Resection of the multiple tumors was performed. One year after the operation the patient was well and abdominal US, CT of the liver and Galium scan showed no mass lesion. On postoperative examination, her serum immunoglobulin (Ig) G, IgA, IgM levels, titers of complement three (C3), four (C4) and total hemolytic complement activity (CH50) were all normal, and Coombs’ test, rheumatoid factor, anti-nuclear antibodies, lupus erythematosus test, thyroid test, microsome test, anti-mitochondria antibodies and anti-smooth muscle antibodies were all negative. Bone marrow aspiration showed no lymphoid cell proliferation.

Pathologic Findings

Macropscopic findings
The resected specimens of the liver were composed of parts of segments two, three, four and six. Among them, a relatively well circumscribed, but not encapsulated grayish-white colored nodule, measuring 1.3x1.5 cm in size, was observed on the cut surface of S6 (Fig. 3).

Microscopic findings
The nodular lesion of S6 showed massive infiltration of lymphoid cells with reactive hyperplastic lymph follicles (Fig. 4A). Several bile ductules and capillaries were observed in the

Fig. 1. Hepatic angiogram demonstrates a tumor stain in segment six of the liver.

Fig. 2. CTAP image shows a round, soft-tissue attenuation perfusion defect in segment six of the liver.

Fig. 3. Cut section of segment six of the liver shows a 1.5x1.3 cm, well-circumscribed, noncapsulated grayish-white nodular lesion.
lesion. The lymph follicles varied in size and shape with germinal centers composed of small and large lymphoid cells and tingible body macrophages (Fig. 4B). The germinal centers were encircled by a thick peripheral layer of small, mature lymphoid cells. Lymphoid cells in the interfollicular space consisted of small, mature lymphoid cells (Fig. 4C).

Immunohistochemistry

Immunohistochemical studies on paraffin-embedded tissue sections using L-26 (monoclonal antibody recognizing pan-B cells), UCHL-1 (monoclonal antibody recognizing pan-T cells), and immunoglobulin antisera specific for κ and λ chains (DAKOPATTS A/S, Glostrup, Denmark) were performed by the avidin-biotin-peroxidase complex (ABC) technique (10). Lymphoid cells positive for L-26 were distributed mainly in germinal centers, while those positive for UCHL-1 were distributed in interfollicular spaces and circumferential sites of the germinal centers. Lymphoid cells showing positive staining for κ and λ chains were observed together.

DNA analysis for IgH gene rearrangement using polymerase chain reaction and consensus primers for complementarity determining region 3 (CDR3) in variable region (11) showed no discrete amplified band in the tumor in the present case (data not shown).

The needle biopsy specimen taken from the liver on April 3, 1992, three weeks before the beginning of IFNα, demonstrated an accumulation of lymphoid cells, some of which formed lymph follicles in portal areas, with a mild degree of piecemeal necrosis and lobular inflammation. The diagnosis was mild chronic active hepatitis.

Discussion

Pseudolymphoma is recognized as a mass lesion with histologic features of diffuse reactive lymphoid proliferation. The common locations of these tumors are the alimentary tract (12, 13), orbit (14), lung (15), skin (16), and thyroid (17). Liver is a rare site for pseudolymphoma. Only two cases have been reported; one is pseudolymphoma of the liver incidentally detected at autopsy in a patient with gastric cancer (18), and the other is one complicated with primary immunodeficiency disease (19). Although the pathogenesis is unknown, pseudolymphoma can develop with autoimmune diseases such as Sjögren’s syndrome (20), by anticonvulsant drugs (21) and following mechanical stimulation (22).

In the present case, the lesions of the liver were composed of massive infiltration of small mature lymphocytes and variable sized multiple lymph follicles with germinal centers. Pathohistological findings of the pseudolymphoma in the present case were compatible with those observed in autoimmune disease- or drug-induced pseudolymphoma. The results of the immunohistochemical stainings also supported the diagnosis of pseudolymphoma. In contrast to immunologically monoclonal B-cell malignant lymphomas which is a common type of primary lymphoma of the liver (23), distribution of T- and B-cells in the pseudolymphoma and its polyclonal immunological pattern are similar to those in reactive lymph nodes (24). A recent report (25), however, demonstrated that Southern blot hybridization analysis for clonal immunoglobulin heavy chain
The liver is a very rare site for pseudolymphoma. The present case demonstrated clinically and pathologically documented chronic active hepatitis B three months before the detection of the liver tumors. The existence of a few lymph follicles in the portal areas of the liver at the biopsy before IFNa treatment makes us speculate a continuity between chronic hepatitis and pseudolymphoma. There have been no reports of pseudolymphoma complicated with hepatitis B. The significance of the presence of lymph follicles in the portal areas is uncertain, however, it is not so rare in the case of chronic hepatitis (26). The possibility that IFNa stimulated the formation of lymph follicles in the present case remains to be proven, although the size of the tumor did not change for two months after cessation of IFNa treatment. A report has shown the association between another rare disease, primary hepatic lymphoma, and HBV infection (27); the authors speculated that the etiology of the hepatic lymphoma may be related to chronic antigenic stimulation from the hepatitis B infection. Although they did not show a pathological continuity between the preceding chronic hepatitis and lymphoma, there is a greater possibility that a similar etiology was involved in the development of pseudolymphoma in the present case.

Drug-induced pseudolymphoma is occasionally reported with drugs such as anticonvulsants (21), and is characterized by the so-called “pseudolymphoma syndrome”. It consists of the triad of fever, generalized rash and lymphadenopathy and is thought to be caused by a hypersensitivity reaction to drugs. In the present case, the pseudolymphoma developed after treatment with huLe-IFNα for two months. The present patient did not show any signs of “pseudolymphoma syndrome” and the lesions were localized in the liver, unlike the disseminated lesions commonly observed in drug-induced pseudolymphoma. This suggests that the etiology of the present pseudolymphoma is unlikely to be associated with a hypersensitivity to huLe-IFNα. IFNα has many potential complications (3), however, to our knowledge, development of lymphoproliferative disorders has not been reported. IFN has various effects on the immune system. It enhances the surface expression of major histocompatibility complex (MHC) class I or II antigens on several cell types that could be targets of autoreactive clones of T-lymphocytes or B-lymphocytes (4, 5). IFNα also acts directly on B lymphocytes to enhance immunoglobulin production (6) and stimulates T-cell cytotoxicity (7) as well as the activity of natural killer cells (8). When these findings are combined, it is possible to speculate that the pseudolymphoma in the present case is the result of a complex immune response of the host to antigens on HBV-infected hepatocytes modified by IFNα.

IFNα may cause autoimmune disease (3) and pseudolymphoma may develop in patients with immune abnormality. The most common finding of pseudolymphoma accompanied by autoimmune disease is generalized lymphadenopathy. Although single organs can be involved (20), liver involvement has not been reported. Because the seroimmunological analysis of the present patient was normal, and she had no past history of autoimmune disease or immunodeficiency disorders, her pseudolymphoma is not likely to be due to some specific immune abnormalities.

IFNα is increasingly used in the treatment of various diseases especially in chronic active hepatitis (1, 2). We diagnosed pseudolymphoma in the liver of a patient receiving IFNα for two months. Although the etiology of the pseudolymphoma is unknown and its development is extremely rare, this disorder should be taken into consideration in the differential diagnosis of space occupying lesions in the liver during IFN treatment.

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