Veno-Occlusive Disease in Hypereosinophilic Syndrome
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A 68-year-old male with hypereosinophilic syndrome developed acute hepatic veno-occlusive disease. The diagnosis of veno-occlusive disease was made mainly based on clinical symptoms and hepatic phlebography. Although veno-occlusive disease caused hepatic failure complicated with massive ascites, consciousness disturbance and coagulation abnormality, all of these manifestations subsided shortly after the start of corticosteroid therapy for hypereosinophilic syndrome. Since eosinophils cause direct tissue damage and local hypercoagulation, it is suggested that hypereosinophilia may be actively involved in the development of hepatic veno-occlusive disease in the course of the disease state.

Key words: eosinophil, eosinophil granule proteins, hepatic venous pressure

Introduction
Hepatic veno-occlusive disease (VOD) of the liver is a hepatotoxic lesion involving obstruction of small intrahepatic veins and damage to the surrounding centrilobular hepatocytes and sinusoids (1). Although fibrous obliteration of small hepatic veins is the characteristic lesion of long-standing VOD, early lesions show no hepatic fibrosis and consist of subendothelial edema, hemorrhage within small central venules and centrilobular congestion with hepatocyte degeneration (1, 2). The pathogenesis of VOD is obscure but most likely is related to endothelial damage and localized activation of the coagulation system (3, 4). The association between small hepatic vein obstruction and eosinophilia has been discussed in patients who received dacarbazine-containing anticancer chemotherapy (5-8), and eosinophil granule proteins are now believed to have potential hypercoagulable effects in addition to tissue-damaging effects (9-11). Although there have been three case reports on hepatic vein obstruction following hypereosinophilic syndrome (HES) since 1985 (12-14), these seem to be Budd-Chiari syndrome associated with HES due to the obstruction at the level of the large hepatic vein. In this report, we describe a case of hepatic VOD which developed in the course of HES.

Case Report
A 68-year-old male was admitted to our hospital on August 27, 1992, with a chief complaint of malaise persisting for one month. There was no history of allergy, parasitic disease, or medication habit. On physical examination, mild hepatomegaly (25 mm on the right midclavicular line) and ascites were noted. The hemoglobin level was 16.7 g/dl, white blood cell count 12,600/μl with 3,780 eosinophils/μl, and platelet count 201,000/μl. The leukocyte alkaline phosphatase level was normal. Other laboratory findings were as follows: aspartate aminotransferase, 46 IU/l; alanine aminotransferase, 87 IU/l; γ-glutamyltranspeptidase activity, 74 IU/l; total bilirubin, 2.39 mg/dl; prothrombin time, 17.6 sec; hepataplastin test, 41%; ammonia 73 μg/dl; α-fetoprotein, 3.6 ng/ml. Serum levels of vitamin B₁₂ and unsaturated B₁₂ binding capacity were 1,553 pg/ml (normal, 240–840 pg/ml) and 1,726 pg/ml (normal, 900–1,400 pg/ml), respectively. Antibody against hepatitis C virus (HCV) was proven to be positive with an enzyme-linked immunosorbent assay (ELISA) method though anti-HCV antibody by an immunoradiometric assay (IRMA) method and HCV-RNA determined by polymerase chain reaction (PCR) were negative. Serum lysozyme levels were within the normal range. Ascitic fluid had characteristics of transudate and contained no eosinophils. The fluid was negative for microorganisms by culture and staining. Bone marrow aspiration and biopsy specimen showed hyperplasia of mature eosinophils. Chromosomal analysis using the G-banding technique showed a normal karyotype with no evidence for bcr-abl rearrangement. Serological and stool tests for parasitic infection were negative. Chest roentgenogram, electrocardiogram, and upper gastrointestinal endoscopy were normal. Echocardiogram revealed a small amount of pericardial effusion, but cardiac function was normal. Ultrasonogram of the abdomen on Sep-
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tember 18, showed hepatomegaly with hypertrophy of the caudate lobe, stenosis of three hepatic veins surrounded by low-echoic areas, and ascites (Fig. 1). Although initial computerized tomographic (CT) scans after the intravenous injection of a contrast agent demonstrated normal liver parenchyma on August 28, postcontrast CT three weeks later (September 18) revealed heterogenous liver parenchyma with high attenuation areas interposed with other areas of low attenuation (Fig. 2). T2-weighted magnetic resonance (MR) images also showed heterogenous liver parenchyma. T2-weighted MR images revealed the presence of stenotic hepatic veins. Scintiscans using 99mTc-phytate colloid showed irregular uptake and apparent filling defects indicating the distortion of the lobular architecture. Celiac angiogram demonstrated normal hepatic artery. Portovenogram following the superior mesentric arterial injection showed no evidence of obstruction in the portal vein but the hepatic filling pattern was mottled. Venacavogram revealed the patent inferior vena cava. On wedged right hepatic venogram, large branches were patent, but the small hepatic radicles were irregularly distributed and replaced by a network of tortuous, narrow and interplacing vessels (Fig. 3). The level of wedged hepatic venous pressure was 33.5 mmHg, which was extraordinarily high compared with free hepatic venous pressure, 9.5 mmHg. The level of central venous pressure was 10.5 mmHg. Liver biopsy was not performed because of intractable massive ascites and coagulation abnormality.

He was treated with prednisolone at a dose of 60 mg/day on September 21, 1992. The eosinophil count dropped substantially by the following day and a good response was achieved; ascites disappeared within the next 2 weeks, serum levels of alanine aminotransferase were normalized by November 2, and all of the coagulation tests returned to normal by November 30. Accordingly, the dose of prednisolone was reduced to 40 mg/day on October 6. He had remained in a complete response state and prednisolone was gradually tapered to 15 mg/day by January 4, 1993.

After the normalization of coagulation tests, the patient underwent percutaneous liver biopsy of the right lobe to evaluate hepatic damage caused by the small hepatic vein obstruction on January 19, 1993. The biopsy specimen disclosed central vein dilatation with dilated pericentral sinusoids, pericentral disruption of the lobular architecture, and subintimal deposition of lipofuscin (Fig. 4). Slight portal fibrosis and minimal mononuclear cell infiltration suggested previous HCV infection. Congestion, necrosis, or perivenular fibrosis was not observed. A new series of CT scans and ultrasonogram, performed in January 1993, showed no abnormality.

When the corticosteroid therapy was discontinued on April...
26, 1994, modest eosinophilia developed again. At a regular follow-up on October 21, 1994, his eosinophil count was increased to 1,044/μl. No specific therapy for the eosinophilia has been instituted because he has not presented with clinical manifestations due to eosinophilic infiltration at the time of this writing.

**Discussion**

In the present case, the association of VOD with HES is unique. The diagnosis of HES was based on the conventionally used criteria (15). Recently the elevation of serum vitamin B12 and unsaturated B12 binding capacity have been reported to be characteristics of HES (16); this finding was observed in the present case. The diagnosis of VOD, which was indicated by clinical as well as histological findings, was confirmed by the hepatic phlebography.

Hepatic phlebography is helpful for the diagnosis of small hepatic vein obstruction as previously described (17, 18). Small hepatic radicles were replaced by an irregular network of fine and tortuous vessels in the present case. This venographic feature was similar to those observed in patients with VOD. The gradient between the wedged hepatic and free hepatic venous pressures was 24 mmHg. A gradient ≥10 mmHg is a predictive value which is as high as 80% positive for the histologic diagnosis of VOD (3). Apart from the pathophysiological features, such a venographic picture in addition to a high pressure gradient indicates obstruction at the level of the small hepatic vein, which is the site of the lesion involved in VOD.

Although fibrous obliteration of central veins which is characteristic of VOD was not found histologically in the present case, liver biopsy after complete remission has been reported to demonstrate normal postrecovery findings without residual fibrosis (2). Furthermore, Schulman et al described that early lesions of hepatic VOD show only subintimal edema, hemorrhage within small central venules and centrilobular congestion with hepatocyte degeneration (1).

The association between small hepatic vein obstruction and eosinophilia has been discussed in patients who have received dacarbazine-containing anticancer chemotherapy (5–8). Since these cases have common histological features including centrilobular necrosis and infiltration of the liver with eosinophils, several authors have postulated that the hepatocyte necrosis provoked by dacarbazine is associated with eosinophilia in the peripheral blood and in the liver (5–7). Despite a wide spectrum of clinical manifestations in HES, small hepatic vein obstruction has never been reported previously.

Although the events initiating human VOD are still controversial, the local activation of the coagulation system in addition to the injury of the endothelial cells, sinusoids and hepatocytes in zone 3 of the liver acinus, has been thought to play an important role in the genesis of VOD (3, 4). Eosinophil granule proteins have been found to have not only tissue-damaging effects but also potential hypercoagulable effects (9–11). Furthermore, activated eosinophils have been reported to release platelet-activating factor which induces platelet aggregation (19). Platelet aggregates, stabilized by fibrin, rapidly form hemostatic plugs at sites of vessel injury or regions where blood flow is disturbed (20). Since in this case the liver dysfunction was closely related to eosinophilia, hypereosinophilic may be actively involved in the development of hepatic VOD in the course of HES.

**References**

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