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Teaching cases

Weil's disease (leptospirosis) manifesting as fulminant hepatic failure: Report of an autopsy case

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ABSTRACT

We report an autopsy case of a 60-year-old man with Weil's disease who died of fulminant hepatic failure. Ante-mortem blood culture yielded the growth of *Leptospira interrogans* (serovar *icterohaemorrhagiae*). At autopsy, the liver weighed 1210 g and showed a typical appearance of "acute yellow liver atrophy". Zone 3 (centrilobular region) showed submassive necrosis of hepatocytes accompanied by marked hemorrhage. Hepatocytes in zones 1 and 2 were well preserved, and the leptospira antigen was immunohistochemically demonstrated in several hepatocytes. Dissociation of liver cell plates was not observed. An immunohistochemical study demonstrated that CD31-positive, sinusoidal endothelial cells had almost completely disappeared in zone 3. This finding suggested that severe and selective damage to endothelial cells in zone 3 was the main cause of the submassive hepatocellular necrosis, which led to fulminant hepatic failure in the present case.

Introduction

Weil's disease (icteric leptospirosis) is a potentially fatal zoonosis which is prevalent mainly in tropical countries and caused by *Leptospira interrogans* (serovar *icterohaemorrhagiae*) infection. It is characterized by a generalized hemorrhagic tendency and occasionally severe damage to many organs, including the liver [3,4], kidney [3,10], skeletal muscle [3,13], lung [3,11,14], and cardiovascular system [3,6]. While there have been many published articles dealing with the histopathology of hepatic lesions in human [3,7,10] and experimental [2] leptospirosis, the pathogenesis of hepatic lesions in Weil's disease has not yet been sufficiently elucidated.

We report here an autopsy case of Weil's disease, in which the patient manifested with fulminant hepatic failure (an unusual clinical feature for Weil's disease). We found submassive centrilobular hepatocellular necrosis associated with intense hemorrhage, and confirmed the almost complete loss of sinusoidal endothelial cells in zone 3 by immunohistochemistry for CD31, suggesting severe, selective damage to these cells. The selective loss of endothelial cells in zone 3 was a characteristic finding in the present case, and a similar finding has not been documented in the previously reported cases of human leptospirosis. We suggest that selective endothelial damage in zone 3 played an important role in the pathogenesis of fulminant hepatic failure in the present case.

Case report

Since the details of the clinical and microbiological findings of this case will be reported in a separate article [12], only a brief clinical summary is given below.

The patient, a 60-year-old Japanese man who worked in a port in Japan, presented with fever and myalgia. Laboratory examination demonstrated thrombocytopenia, and he was treated based on a clinical diagnosis of idiopathic thrombocytopenic purpura. Three months later (midsummer), he was found in a stuporous state in a very hot and humid apartment, and was diagnosed with heatstroke. After emergency admission to our hospital, fever, myalgia, and consciousness disturbance persisted, and a laboratory examination disclosed a generalized inflammatory reaction and hepatic insufficiency. In spite of the administration of antibiotics and corticosteroid, he showed a downhill clinical course and died of multiple organ failure 2 months after admission. One of the samples of blood culture which had been taken 1 month before death yielded the growth of *Leptospira interrogans* (serovar *icterohaemorrhagiae*), but

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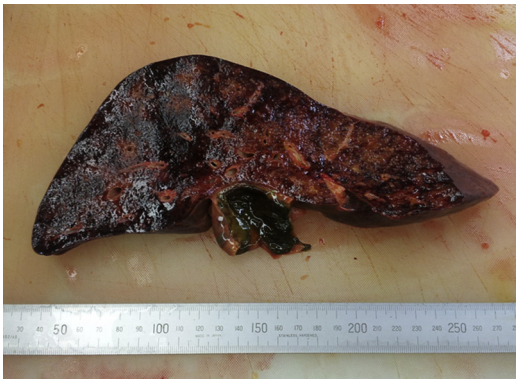

Fig. 1. The cut surface of the liver at autopsy showing a mottled appearance with a red and yellow color, typical of "acute yellow liver atrophy". (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

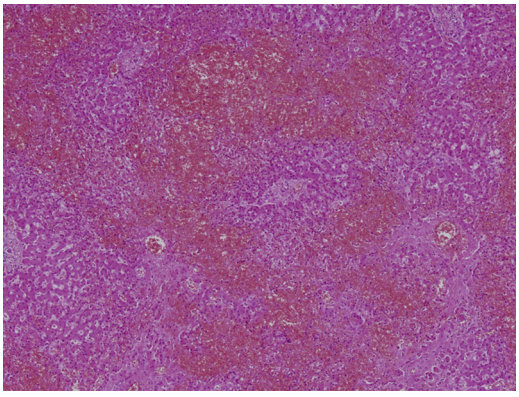

Fig. 2. Submassive necrosis accompanied by extensive, fresh hemorrhage can be noted in zone 3 of hepatic lobules. Liver tissues in zones 1 and 2 are well preserved (hematoxylin-eosin stain, ×10).

this result was obtained 2 days before the death of the patient. Serological tests for infection by hepatitis B or C virus were negative.

Pathological findings

Major pathological findings at autopsy were restricted to the liver, which weighed 1210 g and showed a typical mottled appearance with a red and yellow color, consistent with "acute yellow liver atrophy" (Fig. 1). On microscopic examination, zone 3 of the hepatic lobules showed submassive, confluent necrosis and marked hemorrhage (Fig. 2). Hepatocytes in zone 3 had largely disappeared, leaving only a few necrobiotic hepatocytes (Fig. 3). The infiltration of lymphocytes or neutrophils was lacking, but macrophages showing cytoplasmic swelling or hemophagocytosis were found within the necrotic zone. With reticulin stain, marked collapse of the reticulin framework and an increase of reticulin fibrils were noted in zone 3 (Fig. 4), but collagenization was not seen. In zones 1 and 2, hepatocytes were atrophic, but no degenerative features were found except focal and mild microvesicular steatosis. The hepatocellular cords were well preserved, and no dissociation or disorganization of hepatocytes was seen. Mild dilatation of bile canaliculi with bile plugs was noted focally, but the intracellular deposition of bile pigment was not found.

Immunohistochemical studies were carried out on paraffin sections using the EnVision detection system (Dako), or Simple Stain-Max method (Nichirei), and employing monoclonal or polyclonal antibodies against the following substances: CD31 (clone JC70A, Dako, 1:100), CD34 (clone QBEnd 10, Dako, 1:100), CD68

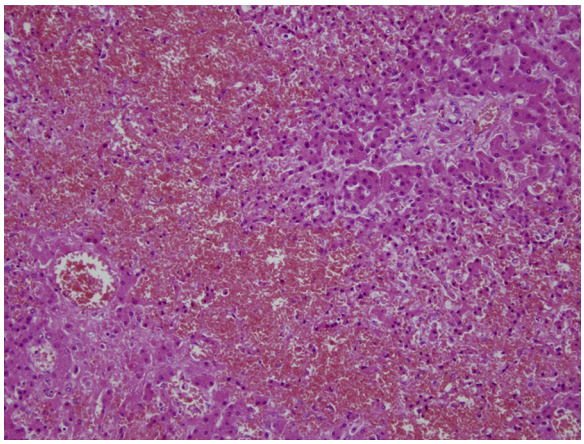

Fig. 3. Higher magnification of Fig. 2 showing the extensive loss of hepatocytes in zone 3 (left) (hematoxylin-eosin stain, ×25).

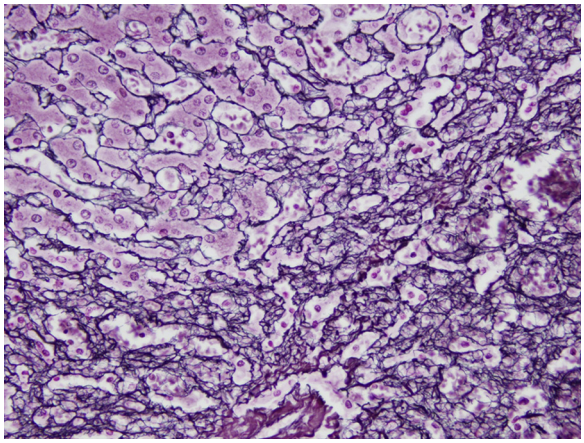

Fig. 4. The reticulin framework in zone 3 showing marked collapse (lower right) with an increase and aggregation of reticulin fibrils (reticulin stain, ×50).

(clone KP1, Dako, 1:100), CD163 (clone 1OD6, Thermo Scientific, 1:200), CD204 (clone SRA-E5, TransGenic, 1:200), alpha-smooth muscle actin (SMA) (clone 1A4, Dako, 1:100), desmin (clone D33, Dako, 1:100), cleaved caspase 3 (polyclonal, Cell Signaling, 1:100), cleaved vimentin (polyclonal, MBL, 1:100), Ki67 (clone MIB-1, Dako, 1:100), and the leptospira antigen (R2 antibody, 1:500, kindly donated by Prof. Shin-ichi Yoshida, Department of Bacteriology, Faculty of Medical Sciences, Kyushu University).

CD31-positive, sinusoidal endothelial cells selectively disappeared in zone 3 (Fig. 5). In zones 1 and 2, endothelial cells were well preserved, and, in addition, CD34-positive endothelial cells were scattered, which suggested focal "capillarization" of the sinusoids. Using antibodies against macrophage markers or scavenger receptors (CD68, CD163, and CD204), macrophages (Kupffer cells) were also found to be decreased in number in zone 3 in comparison with those in zones 1 and 2 (Fig. 6). With antibodies against alpha-SMA and desmin, the activation of hepatic stellate cells (fat-storing cells or Ito cells) was not observed in zone 3. With antibodies against well-established markers of apoptosis, cleaved caspase 3 and cleaved vimentin, no increase of apoptosis of sinusoidal endothelial cells was demonstrated in zone 3, although a small number of apoptotic cells were found among hepatocytes and macrophages throughout the hepatic lobules. Cell proliferation activity was estimated using an anti-Ki67 antibody. An increase of Ki67-labeling index was not found in zone 3. Although leptospires were not detected using Warthin-Starry stain in tissue sections of the liver, kidney, and lung, a granular immunoreactivity for the