Liver Involvement in Tsutsugamushi Disease

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KANNO, A., YAMADA, M., MURAKAMI, K. and TORINUKI, W. *Liver Involvement in Tsutsugamushi Disease*. Tohoku J. Exp. Med., 1996, 179 (3), 213-217
——— Tsutsugamushi disease, one of the rickettsiosis, is known to be occasionally accompanied by elevation of hepatic enzyme levels. However, there are only a few reports on histopathological findings of the liver. We presented a case of Tsutsugamushi disease with liver involvement. A 51-year-old man suffered from eruptions and a high fever with a mild transaminasemia. He was diagnosed as Tsutsugamushi disease by detection of IgM class antibody against *Rickettsia tsutsugamushi*. Laparoscopic examination showed a dark-brown liver with diffuse whitish markings. Microscopic findings were consistent with the features of non-specific reactive hepatitis: sinusoidal small lymphocyte infiltrations, mild disarray of hepatocytes and aggregation of T lymphocytes and macrophages in the lobule. ——— Tsutsugamushi disease; rickettsiosis; liver disease

Tsutsugamushi disease, so-called scrub typhus, prevails in Japan as well as pacific islands and southeast Asian countries. Although the morbidity decreased since 1965, there has been a remarkable resurgence since 1976 in Japan (Kawamura and Tanaka 1988). The causative agent is *Rickettsia tsutsugamushi* (*R. tsutsugamushi*) which transmits via a mite as the vector. The major clinical signs are a fever and a skin lesion (Berman and Kundin 1973). Especially, scab at the bite of a mite is characteristic (Allen and Spitz 1945). Although it is well known that elevation of hepatic enzyme levels is frequently observed in patients with Tsutsugamushi disease (Berman and Kundin 1973), there are only a few reports on the histopathological features of the liver (Allen and Spitz 1945; Satoh et al. 1991).

We present a case of Tsutsugamushi disease with a histologically proven liver disease by laparoscopic examination.

Received March 23, 1996; revision accepted for publication May 7, 1996.

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CASE REPORT

A 51-year-old man, who lived in Miyagi prefecture located in the northern part of the Main Island of Japan, visited Natori Chu-ou Hospital on November 16, 1994, with a 4-day history of fever. Physical examination showed eruptions on the trunk. Liver function tests, which had been normal at the medical health check performed 15 months earlier, showed abnormal results. He had no history of blood transfusion, intravenous drug abuse, alcoholism or having a hepatotoxic drug. There was no family history of the liver disease. The hepatic enzyme levels gradually raised, and then he was referred to our hospital on November 25. Physical examination revealed a round exanthema with a central scab on the flexion site of the left knee joint. Laboratory findings were follows: bilirubin 0.6 mg/100 ml (normal range, 0.3–1.0 mg/100 ml), aspartate aminotransferase 295 U/liter (normal range, <35 U/liter), alanine aminotransferase 271 U/liter (normal range, <34 U/liter), lactate dehydrogenase 951 U/liter (normal range, 212–386 U/liter), alkaline phosphatase 514 U/liter (normal range, 105–262 U/liter), γ -glutamyltranspeptidase 102 U/liter (normal range, 5–42 U/liter), total protein 7.6 g/100 ml (normal range, 6.5–8.5 g/100 ml), white blood cell count 10,400/ μ l (normal range, 4,000–8,000/ μ l). Atypical lymphocytes were also found. The coagulation test was unremarkable. We suspected Tsutsugamushi disease from the skin lesions and the fact that he had gone to the neighboring dam to cut the grass 5 days before running fever, and then immediately started an antibiotic therapy with minocycline. After treatment, the fever discontinued within 2 days and the biochemical abnormalities normalized on December 13. The eruptions also turned to be pigmented. On admission, although a Weil-Felix reaction to *Proteus* OX-K was negative, an antibody against *R. tsutsugamushi* was positive by the immunoperoxidase method (Gilliam: IgG $\geq$ 40,960, IgM 10,240; Karp: IgG $\geq$ 40,960, IgM 10,240; Kato: IgG $\geq$ 40,960, IgM 10,240). IgM antibodies against cytomegalovirus and the capsular antigen of Epstein-Barr virus were negative. Hepatitis B surface antigen, IgM antibodies against hepatitis B core and hepatitis A virus, and an antibody against hepatitis C virus were also negative.

Laparoscopic examination with liver biopsy was performed with an informed consent on December 14. Macroscopically, a dark-brown liver with diffuse whitish markings were observed (Fig. 1). The edge of the right lobe partly adhered to the omentum. Upon histopathological examination with hematoxylin and eosin staining, mild disarray of hepatocytes with pale cytoplasm and an increase of small lymphocytes in sinusoids were observed. Many of the hepatocytes were swollen and the nuclei varied in size. Bi- or triple-nucleated hepatocytes were also seen. Fat deposition in hepatocytes was observed around the central vein. In some places of hepatic lobules, aggregation of inflammatory cells was sparsely found (Fig. 2). It was revealed that the aggregating cells

Fig. 1. Laparoscopic examination in a patient with Tsutsugamushi disease. A dark-brown liver with diffuse whitish markings was observed.

Fig. 2. Representative histopathology of the liver. In the hepatic lobule, an aggregation of mononuclear cells was found. Many small lymphocytes in sinusoids and binucleated hepatocytes were seen around the lesion. Hematoxylin and eosin, $\times 200$.

consisted mainly of T lymphocytes and macrophages by using the avidin-biotin-peroxidase complex method with monoclonal antibodies to T lymphocyte, B lymphocyte and macrophage. There were no pathological changes in portal tracts. The causative agent, *R. tsutsugamushi*, could not be detected in the liver by microscopical observation with Giemsa staining nor by electron microscopic examination.

DISCUSSION

We suspected that our patient had been infected with *R. tsutsugamushi* by the bite of a mite at the dam 5 days before the attack of fever. However, the day of infection could not be exactly determined, because the idea that the incubation period of Tsutsugamushi disease is 9–18 days is generally accepted (Burnett 1980). Although the antibody to *R. tsutsugamushi* was detected by the immunoperoxidase method, the Weil-Felix reaction to Proteus OX-K was negative in this study. It is known that the Weil-Felix test is positive in patients with Tsutsugamushi disease, but not in all (Berman and Kundin 1973). The immunoperoxidase method is sensitive and recommended to be used for the diagnosis of Tsutsugamushi disease.

Although it is known that liver dysfunction is occasionally accompanied with Tsutsugamushi disease (Berman and Kundin 1973), there have been only a few reports on the histopathological features of the liver (Allen and Spitz 1945; Satoh et al. 1991). Furthermore, the laparoscopic findings have not yet been described. In the present laparoscopic study, whitish markings on the surface of the liver and the perihepatic adhesion were found in a patient with Tsutsugamushi disease. These macroscopic findings may be compatible with perihepatitis (Kundin et al. 1964; Catanzaro et al. 1976). Microscopic changes such as disarray of hepatocytes, double- or triple-nucleated hepatocytes, fat deposition in hepatocytes, sinusoidal infiltration of small lymphocytes, and aggregation of mononuclear inflammatory cells were regarded as non-specific reactive hepatitis (Allen and Spitz 1945; Catanzaro et al. 1976; Hwang et al. 1993), and it is suggested that injury and regeneration of hepatocytes with inflammatory reaction were certainly progressing in the liver of the patient with Tsutsugamushi disease. Although it has been reported that granuloma formation was characteristic phenomenon in autopsied or biopsied liver of patients with Tsutsugamushi disease (Allen and Spitz 1945; Satoh et al. 1991), it was not seen in our patient. Because the liver biopsy was taken one month later the onset of illness when the liver function test had been normal, the histological changes of the liver might be mild in this case. According to the fact that aggregating inflammatory cells in the hepatic lobules, which probably accompanied focal hepatocyte necrosis, were mainly T lymphocytes and macrophages, the cellular immunity may be attributed to the pathogenesis of the hepatic injury. However, it needs further investigation to verify the mechanism of liver injury induced by *R. tsutsugamushi*.

Until the characteristic skin lesion, eschar, was revealed by our physical examination of the whole body, the present patient had not been regarded as Tsutsugamushi disease. If the appropriate treatment with minocycline was delayed a more few days, the life-threatening complication of multiple organs might occur (Allen and Spitz 1945; Berman and Kundin 1973).

Acknowledgments

We thank Dr. Kazuo Akiyama for testing the antibody to *R. tsutsugamushi*, and Dr. Atsushi Horaguchi for providing the clinical data.

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