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Case Report

A Transient Emergence of Hepatic Granulomas in a Patient with Chronic Hepatitis B

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KANNO, A. and MURAKAMI, K. *A Transient Emergence of Hepatic Granulomas in a Patient with Chronic Hepatitis B.* Tohoku J. Exp. Med., 1998, **185** (4), 281-285 —— So far there were no reports but one on a hepatic granuloma in chronic hepatitis B virus (HBV) infection. We present a case of chronic hepatitis B with a transient emergence of hepatic granulomas. The case was a 35-year-old male who had chronic hepatitis with persistent hepatitis B surface antigen in the sera. A liver biopsy showed noncaseating granulomas in the parenchyma and a mild portal enlargement with mononuclear cell infiltration. The cellular components of the granulomas were mainly cluster of differentiation 68-positive macrophages with a few lymphocytes in the periphery. However, no granulomas were found in a liver specimen obtained three weeks after the first liver biopsy. Possible disorders causing hepatic granulomas such as tuberculosis, sarcoidosis, drugs and other infectious diseases were ruled out by clinical, serological and histopathological examination. Thus it is possible that the transient emergence of hepatic granulomas is a phenomenon related to chronic HBV infection. ———— hepatic granuloma; chronic hepatitis B

A hepatic granuloma is thought to be a result of localized inflammatory immune response to inciting agents. It is mainly composed of mature macrophages with lymphocytes in the rim (MacSween 1987). Hepatic granulomas are found in miscellaneous diseases including infections, foreign substrate-associated diseases, and systemic diseases such as sarcoidosis and Hodgkin's disease (Reynold et al. 1990). They are also found in primary liver disease including primary biliary cirrhosis, drug-induced hepatitis (Sartin and Walker 1991), and hepatitis C virus-related chronic liver disease (Emile et al. 1993). So far, however, there have been no reports but one (Goldin et al. 1996) on the emergence of hepatic granulomas in chronic hepatitis B.

We present one such patient in whom hepatic granulomas appeared during the course of chronic hepatitis B infection.

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Case Report

A 35-year-old man, in whom liver dysfunction was pointed out at a medical health checkup, was referred to our hospital on September 24, 1996. He was free of subjective symptom. He had no history of receiving a blood transfusion, intravenous drug abuse or alcoholism. He had no hepatotoxic drugs.

Laboratory findings were as follows: Bilirubin 0.5 mg/100 ml (normal range, 0.3–1.0 mg/100 ml), aspartate aminotransferase 129 U/liter(normal range, <35 U/liter), alanine aminotransferase (ALT) 298 U/liter (normal range, <34 U/liter), lactate dehydrogenase 234 U/liter (normal range, 212-386 U/liter), alkaline phosphatase 256 U/liter (normal range, 105-262 U/liter), γ-glutamyl transpeptidase 76 U/liter (normal range, 5-42 U/liter), total protein 7.5 g/100 ml. Other laboratory findings were not remarkable. Serological examination showed that hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) was positive by a radioimmunoassay. Both antibodies to HBsAg and HBeAg were negative. It was suggested that he had been chronically infected with hepatitis B virus (HBV), because antibody to hepatitis B core antigen (HBcAg) was present in a high titer. The activity of serum HBV DNA polymerase was negative, but HBV DNA was positive by chemiluminescent DNA-RNA hybridization using a 3200 base RNA probe (Viraprobe HB Lumi, TFB Co., Tokyo).

A percutaneous liver biopsy was performed on October 7, 1996. The prepared specimen contained nineteen portal tracts. A mild fibrous portal enlargement with mononuclear cell infiltration and focal hepatocellular necrosis were found. There were few acidophilic bodies. Noncaseating granulomas were diffusely distributed in the parenchyma, with several giant cells. The number of granuloma ranged from two to five in each hepatic lobule. There were a few

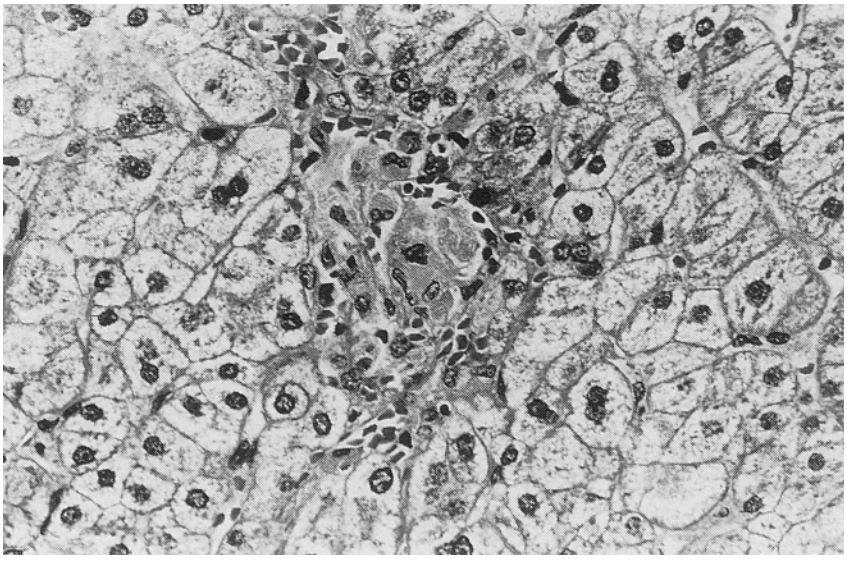

Fig. 1. The liver specimen shows a noncaseating granuloma, which is composed of macrophages. Hematoxylin and eosin, $\times 400$.

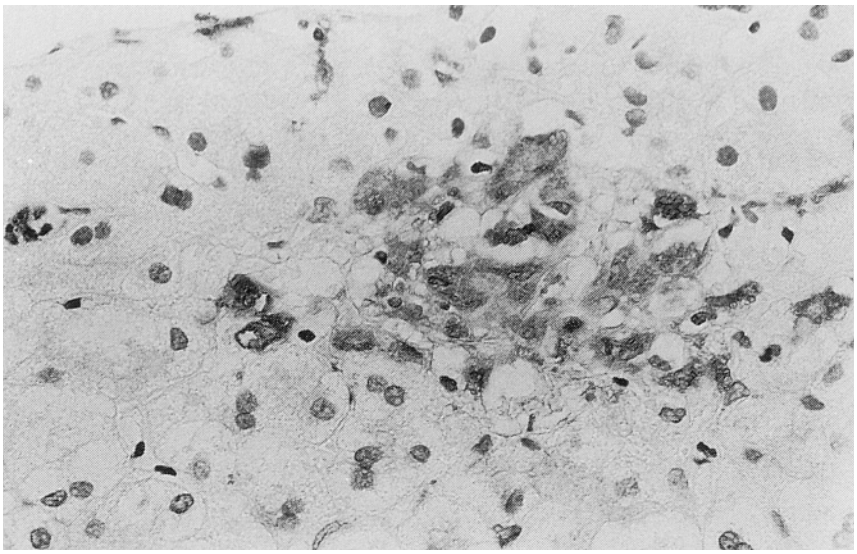

Fig. 2. The cellular components of the granuloma are positive for CD 68. The avidin-biotin-peroxidase complex method, ×400.

lymphocytes in the periphery of the granulomas (Fig. 1).

The cellular components of granulomas were mainly cluster of differentiation (CD) 68-positive macrophages, which were demonstrated by immunohistochemistry using mouse monoclonal antibody to CD 68 (DAKO Japan Co., Ltd., Kyoto) (Fig. 2). They contained no ceroid pigment, and periodic acid-Schiff stain after diastase digestion was negative either.

No acid-fast bacilli were demonstrated. Neither HBsAg nor HBcAg was found by immunohistochemical examination using goat polyclonal antibody to HBsAg (DAKO Japan Co., Ltd.) and rabbit polyclonal anti-HBc (DAKO Japan Co., Ltd.), respectively. Further serological examination showed that antibodies to hepatitis A virus, hepatitis C virus, herpes simplex virus, leptospira and *Coxiella burnetti* were negative. IgM class antibodies to Epstein-Barr virus and cytomegalovirus were also negative. Anti-nuclear antibody was negative.

Abdominal ultrasonic examination showed mild enlargement of the spleen. Although a purified protein derivative skin test was positive, a sputum culture for *Mycobacterium tuberculosis* showed a negative result. x-Ray films of the chest revealed no pulmonary changes or a hilar lymphadenopathy. Serum angiotensin converting enzyme level was normal.

On October 14, 1996, recombinant interferon (IFN) α was administrated with a daily intramuscular injection of 9 million units. On the next day, it was revealed that biopsies of a gastric erosion which had been found by upper gastrointestinal endoscopy four days before showed adenocarcinoma. The IFN therapy was immediately stopped, because a surgical treatment for the early gastric cancer was given priority. Thereafter ALT concentrations decreased to near normal levels.

A wedge liver biopsy was taken surgically on October 28, 1996 while gas-

trectomy was performed. There were 39 portal tracts in the prepared specimen. Moderate portal inflammation with fibrosis and focal hepatocellular necrosis were found. Acidophilic bodies were also found. However, there were no granulomas or giant cells. HBsAg and HBcAg were demonstrated in the cytoplasm and in the cytoplasm with or without nucleus of hepatocytes, respectively.

Discussion

Hepatic granulomas are found in a wide spectrum of disorders including infectious diseases, foreign substrate-associated diseases, and systemic diseases such as sarcoidosis and Hodgkin's disease (Reynold et al. 1990). Primary biliary cirrhosis, drug-induced hepatitis (Sartin and Walker 1991), and viral hepatitis including chronic hepatitis C (Emile et al. 1993) and acute hepatitis A (Yamamoto et al. 1995) also accompany hepatic granulomas. However, above mentioned disorders causing possibly hepatic granulomas including drugs, sarcoidosis, tuberculosis, Q fever, leprosy, brucellosis and other infectious diseases were ruled out in this case by clinical serological and histological findings. Thus the granulomas were probably associated with chronic HBV infection. There is only one report on granulomas in chronic HBV liver disease (Goldin et al. 1996). However, a detail information about the histological feature was not described in the literature.

In general, granulomas are thought to be formed by a proliferative inflammatory reaction to pathogens (Adams 1976), which persist until the inciting agent is destroyed. The hepatic granulomas were transiently formed in the present case, probably due to an immunological reaction to HBV or HBV-related agents. It is interesting that he had gastric cancer. However, cancer was not likely to be implicated in the transient emergence of granuloma, because it existed not only at the first liver biopsy but also at the time of operation when the second liver biopsy was performed.

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