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Hepatocellular Carcinoma Infiltrated with Non-Hodgkin's Lymphoma: Report of a Case

TOHRU UTSUNOMIYA[1], MASAHIRO OKAMOTO[1], EIJI TSUJITA[1], MANABU YAMAMOTO[1], SHINICHI TSUTSUI[1], MEGUMU FUJIHARA[2], and TERUYOSHI ISHIDA[1]

Departments of [1]Surgery and [2]Pathology, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Hiroshima, Japan

Abstract
A 70-year-old woman diagnosed to have a hepatitis C virus (HCV) infection was referred to our hospital because of a solitary liver tumor. She underwent a partial hepatectomy, and the tumor was histologically diagnosed as a hepatocellular carcinoma (HCC). In addition, a focal follicle consisting of atypical lymphoid cells was seen within the HCC. Two months later, she was readmitted because of weakness and rapidly developing abdominal fullness. An abdominal computed tomography scan showed widespread tumors with ascites. A cytological examination of the ascites showed large-sized atypical lymphoid cells. An immunohistochemical stain confirmed that the atypical lymphoid cells within the HCC were positive for the CD20 antigen. Taking these findings into account, the hepatic tumor was determined to be a HCC infiltrated with diffuse large B-cell lymphoma. The coexistence of HCC and non-Hodgkin's lymphoma (NHL) is extremely rare. We herein report a case of HCC infiltrated with NHL.

Key words Hepatitis C virus · Hepatocellular carcinoma · B-cell lymphoma · Tumor-to-tumor metastasis

Introduction

Hepatocellular carcinoma (HCC) is a long-term adverse outcome of a hepatitis C virus (HCV) infection, but there is no apparent evidence that HCV has direct oncogenic effects on hepatocytes. Recently, a strong association of non-Hodgkin's lymphoma (NHL) with HCV was reported.[1,2] The liver involvement of NHL has also frequently been observed.[3] However, the coexistence of HCC and NHL in the same patient is extremely rare.[4–6] We herein report a case of HCC infiltrated with NHL.

Reprint requests to: T. Utsunomiya, Department of Surgery, The University of Tokushima, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
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Case Report

In September 2006, a 70-year-old Japanese woman diagnosed with both an HCV infection and diabetes mellitus was referred to our hospital because of a solitary liver tumor. She had a history of blood transfusion for the treatment of anaplastic anemia 30 years ago. Abdominal ultrasonography (US) and a computed tomographic (CT) scan showed a mass with dimensions of 3 cm in diameter in the S5 region of the cirrhotic liver. Moderate splenomegaly was also observed. Her blood count was 2700 leukocytes/mm^3, hemoglobin of 12.7 g/dl, and 54 000 platelets/mm^3. The prothrombin time was in the normal range. Her albumin level was 3.4 g/dl; total bilirubin, 0.7 mg/dl; alanine aminotransferase, 14 IU/l; lactate dehydrogenase, 224 IU/l. The indocyanine green retention test at 15 min was 30.6%. The HCV genotype was 2a and the viral load was higher than 5100 kIU/ml. The levels of serum α-fetoprotein (AFP) 13.1 ng/ml (normal, <10 ng/ml) and protein induced by the absence of vitamin K II (PIVKA II) 237 mAU/ml (normal, <40 mAU/ml) were elevated. She underwent a partial hepatectomy and a cholecystectomy in November 2006. No ascites or lymphadenopathy was observed in the peritoneal cavity. Intraoperative US did not show any other hepatic nodules than the solitary tumor, which was preoperatively detected in the liver. The macroscopic finding of the resected tumor indicated an ordinary HCC in the cirrhotic liver. Histologically, the tumor was diagnosed to be a well to moderately differentiated HCC (pT2, N0, M0: stage II, International Union Against Cancer). In addition, a focal follicle consisting of atypical lymphoid cells was

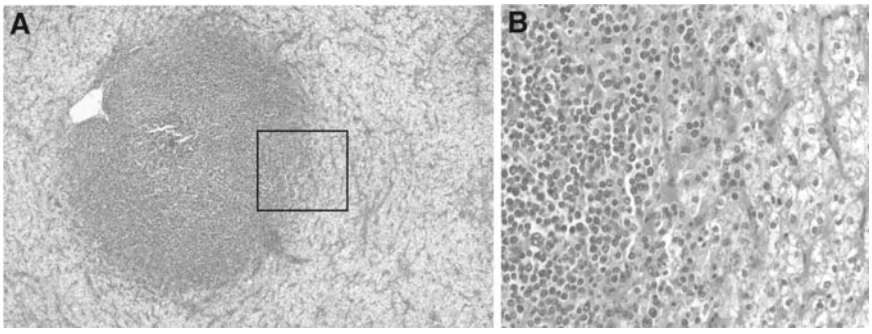

Fig. 1A,B. Histological examination revealed a focal follicle of atypical lymphoid cells in the resected liver tumor. **A** Low-power field (×40); **B** high-power field (H&E, ×100)

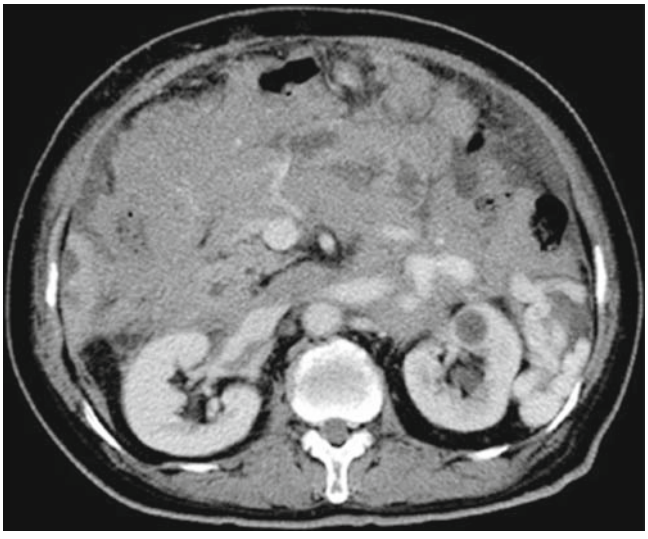

Fig. 2. Computed tomographic scan revealed a widespread tumor involvement of the mesentery, omentum, and retroperitoneum with ascites

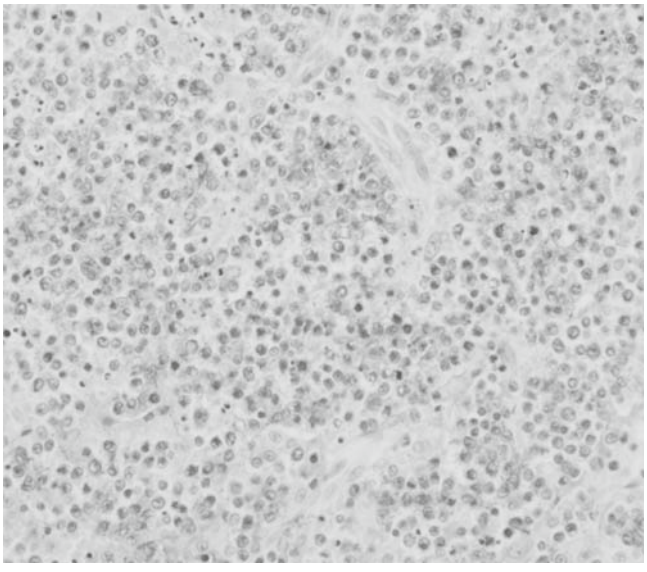

Fig. 3. The atypical lymphoid cells within the tumor were immunopositive for the CD20 antigen (×100)

seen within the HCC (Fig. 1A and B). The clinical significance of these atypical lymphoid cells could not be determined at this time. The patient's postoperative course was uneventful, and she was discharged on postoperative day 10. On January 2007, the patient was readmitted to our hospital because of weakness and rapidly developing abdominal fullness. The serum levels of AFP and PIVKA II were within the normal limits. Alanine aminotransferase was normal while lactate dehydrogenase (749 IU/l) was elevated. An abdominal CT scan showed widespread tumor involvement of the mesentery, omentum, and retroperitoneum with ascites (Fig. 2). The primary site of the disease could not be determined. A cytological examination of the ascitic fluid (chylous ascites) showed large-sized atypical lymphoid cells. Subsequent immunohistochemical staining confirmed the atypical lymphoid cells within the HCC, which had been previously removed, to be positive for the CD20 antigen (Fig. 3) and negative for the CD3, CD10, and MPO antigens. Taking these findings into account, the hepatic tumor in this patient was considered to be an HCC infiltrated with diffuse large B-cell lymphoma, which had not been clinically diagnosed before the hepatic resection. On re-examination of the resected liver tissue specimen, only one other focal follicle of atypical lymphoid cells was found in the region of noncancerous liver tissue. The patient died in February 2007 due to a rapid progression of lymphoma. No autopsy was performed.

Discussion

Several studies have reported an increased prevalence of HCV among patients with NHL. A direct oncogenic role of HCV through B-lymphocyte infection was proposed as the virus is lymphotropic, but this has never been proven. Therefore, the mechanism for HCV-mediated lymphomagenesis may most likely involve chronic B-lymphocyte stimulation through specific immune-related interactions.[7] The differences between specific HCV genotypes with respect to lymphomagen-

esis have been suggested, with genotype 2a being slightly more common than 1b, which is consistent with our patient. Although chronic HCV infection may be associated with the pathogenesis of both HCC and NHL, the coexistence of HCC and NHL in the same patient is extremely rare.[4–6] Only four cases of the coexistence of HCC and NHL in the liver have been previously documented.[8] Three of four cases had cirrhotic liver and one had nodular regenerative hyperplasia. None of these four cases had HCV infection, but two cases had hepatitis B infection. The present case had HCV-related liver cirrhosis.

The metastasis of one tumor into another, referred to as "tumor-to-tumor metastasis," is quite uncommon. Generally the most frequent donor tumor tends to be a lung cancer, and the most common recipient tumor is a renal cell carcinoma.[9] To date, no case of HCC as a donor tumor or a recipient tumor of "tumor-to-tumor metastasis" has been reported. On the other hand, NHL rarely infiltrates into other tumors. Only one such tumor has been previously reported in renal cell carcinoma, which had been infiltrated with NHL.[10] To our knowledge, this is the first reported case of HCC infiltrated with NHL.

The present case indicates that NHL can infiltrate into another tumor, and that such a recipient tumor may therefore possibly be removed with a curative intent, without realizing that the patient has NHL. In such a case, the initial clinical manifestation of NHL may be an infiltration to the recipient tumor. Even if preoperative imaging modalities and laboratory data do not demonstrate evidence of NHL, it is strongly recommended that additional examinations, such as positron emission tomography, be performed immediately after detecting the presence of any focal follicles of atypical lymphoid cells in resected tissue specimens.

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