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CASE REPORT

Hepatocellular carcinoma with chronic B-type hepatitis complicated by autoimmune hemolytic anemia: A case report

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Abstract

A 57-year-old man consulted a local hospital because of a persistent slight fever. At the age of 37 years he was diagnosed having B-type hepatitis, but left the liver dysfunction untreated. Twenty years later, he was diagnosed having chronic hepatitis B, hepatocellular carcinoma (HCC) and macrocytic anemia, and referred to our hospital for further investigation. A HCC with a maximum diameter of 5.2 cm was detected in segment 8. Results of blood tests included 1.8 mg/dL serum total bilirubin, 0.9 mg/dL bilirubin, less than 10 mg/dL haptoglobin, 7.9 g/dL hemoglobin, 130 fL MCV, and 14.5% reticulocytes. A bone marrow sample showed erythroid hyperplasia. The direct Coombs test gave a positive result. We diagnosed the anemia as autoimmmune hemolytic anemia (AIHA), for which prednisolone could not be administered due to positivity for HBsAg and HBeAg. After preparation of washed blood cells for later transfusion, the patient underwent systematic resection of segment 8. The cut surface of the resected specimen demonstrated an encapsulated yellow-brownish tumor measuring 52 mm × 40 mm which was diagnosed pathologicaly as moderately differentiated HCC. On the 9th postoperative day, the patient's temperature rose to 38℃, and exacerbated hemolysis was observed. The maximum total bilirubin value was 5.8 mg/dL and minimum hemoglobin level was 4.6 g/dL. He tolerated this period without blood transfusion. Currently he is being followed up as an outpatient, and shows no signs of HCC recurrence or symptoms of anemia. AIHA associated with HBV infection has been described in only three previous cases, and the present case is the first in which surgery was performed for accompanying HCC.

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Key words: Hepatocellular carcinoma; B-type hepatitis; Auto-immune hemolytic anemia

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a disease characterized by hemolysis caused by auto-antibodies targeting erythrocytes, and is exacerbated by stress[1]. In this report, we describe a patient with AIHA who underwent resection of a hepatocellular carcinoma (HCC), but subsequently showed improvement of anemia.

CASE REPORT

A 57-year-old man consulted a local hospital because of a slight fever for 2 wk. At the age of 37 years, he was diagnosed having liver dysfunction due to B-type hepatitis, but had left it untreated for 20 years. His blood chemistry data showed liver dysfunction and macrocytic anemia, and a liver tumor was found by abdominal ultrasonography. He was, therefore, referred to our hospital in November, 2003.

On physical examination, his conjunctivae were anemic. The liver was palpable one finger-breadth below the right costal margin, but the spleen was not palpable. His family history showed that his elder brother died of liver disease at the age of 53, but the details were unknown. The patient underwent abdominal surgery twice (appendectomy for appendicitis at the age of 19 and cholecystectomy for cholelithiasis at 35) and received no blood transfusion prior to admission to our hospital.

Blood tests revealed impaired liver function, hemolysis and macrocytic anemia (Table 1). The AFP and PIVKA Ⅱ levels were also high. The indocyaningreen (ICG) retention rate at 15 min was 13%. HBs antigen, HBs antibody, Hbe antigen, HBe antibody and HBc antibody were positive. HBV-DNA PCR showed viral proliferation. Serological tests for syphilis, HCV antibody, antinuclear and anti-DNA antibodies, HAM test and sugar water test all gave negative results. However, direct and indirect Coombs tests gave positive results, and the cold agglutinin titer increased 256-fold. A bone marrow sample showed erythroid hyperplasia.

Abdominal ultrasonography and computed tomography

Table 1 Blood test data

AST	67 U/L	WBC	2700×10^6/L
ALT	64 U/L	RBC	199×10^{10}/L
LDH	318 U/L	Reticulocyte	14.5%
(LDH1: 36.1%, LDH2: 34.2%)		HGB	7.9 g/dL
T. Bil	1.8 mg/dL	HCT	23.6%
(D.Bil: 0.9 mg/dL, I.Bil: 0.9 mg/dL)		MCV	130 fL
TP	6.2 g/dL	PLT	6×10^9/L
Alb	3.8 g/dL	PT%	68%
ICGR15	13%	HBsAg	69 COI
AFP	869 ng/mL	HBsAb	172 COI
PIVKA-II	301 AU/mL	HBeAg	108 COI
Direct Coombs test	Positive	HBeAB	40 Inh%
Anti-nuclear antibody	Negative	HBcAb	100 Inh%
HAM test	Negative	HBV-DNA PCR	5.9 LGE/mL
Sugar water test	Negative	TPHA	Negative
Cold agglutinin titer	256 times	HCVAb	Negative

(CT) revealed a liver tumor with a maximum diameter of 5.2 cm in segment 8, which was enhanced by contrast material (Figure 1A). Abdominal angiography showed a hypervascular liver tumor (Figure 1B), but portography demonstrated no abnormality.

Under a diagnosis of HCC, chronic B-type hepatitis and AIHA, the patient underwent systematic resection of segment 8. The operation time was 5 h 42 min and bleeding volume was 642 mL. Blood transfusion was not required.

The cut surface of the resected liver specimen (S8) demonstrated an encapsulated yellow-brownish tumor measuring 52 mm × 40 mm (Figure 2). Histology showed the characteristics of HCC with moderately differentiated neoplastic cells in a trabecular pattern. The tumor was solitary, but as vascular invasion was present, the classification was T2N0M0 according to the UICC Manual of Clinical Oncology (English Edition)[2].

The patient recovered steadily, but on the 9th postoperative day, his temperature rose to 38℃, and antibiotics were administered. At the same time, exacerbation of hemolysis was observed, the maximum total bilirubin value was 5.8 mg/dL and minimum hemoglobin level was 4.6 g/dL. He tolerated this period without blood transfusion, and the symptoms gradually improved over the course of about one week. On the 26th postoperative day, he received two units of washed blood cells due to increased activity and was discharged three days later (Figure 3).

For treatment of B-type hepatitis, lamivudine (100 mg/d) was administered from the 29th postoperative day, and the blood tests for HB virus subsequently became negative about four months later. Because of improvement of the anemia with a hemoglobin level of 9.3 g/dL 9.7 g/dL, prednisolone was not administered for treatment of AIHA after surgery. The patient is currently being followed up as an outpatient, and shows no signs of HCC recurrence.

DISCUSSION

AIHA is a disease in which erythrocytes are injured by an auto-antibody that reacts with an antigen on the erythrocyte membrane. This results in both intra- and extravascular hemolysis, and anemia[1]. AIHA is classified into "warm" or "cold" AIHA according to the temperature at which the antibody acts. IgG or complement on erythrocytes can be detected by direct Coombs test. Several reasons for the appearance of auto-antibody have been suggested. (1) Erythrocytes are recognized as "non-self" as a result of a change of their surface antigen; (2) An antibody originally directed to an invasive microorganism cross-reacts with an erythrocyte antigen; (3) Immunity tolerance fails due to an abnormality of the immunity response system; (4) The clone responsible for producing an auto-antibody increases in a monoclonal or polyclonal manner. However, the fundamental causes or mechanisms are unclear.

AIHA has been reported to be associated with several liver diseases, including autoimmune hepatitis in 15 cases[3-7], C-type hepatitis in 11[8-18], B-type hepatitis in 2[19,20], cytomegalovirus hepatitis in one[21], and A-type hepatitis in 1[22]. Autoimmune responses may play a major role in inducing the combination of the two diseases.

Furthermore, there are a number of reports of HBV infections associated with polyarteritis nodosa, membranous glomerulonephritis, and Gianotti disease[23,24]. An autoimmune reaction participates in all these diseases.

Anemia deteriorated in 6 of 11 patients with C-type hepatitis complicated by AIHA, because of interferon therapy for chronic active C-type hepatitis. These findings suggest that activation of the immunological response can lead to production of auto-antibody directed against erythrocytes, thus worsening AIHA. Before presentation, our patient had suffered from chronic HBV infection for at least 20 years. Therefore, it can be speculated that the patient's immune response was stimulated by HBV, thus contributing to production of the anti-erythrocyte antibody and induction of AIHA.

The primary treatment for AIHA is steroid medication. If this is ineffective, splenectomy or an immunosuppressant can be considered instead. Although treatment of AIHA before surgery may be advisable, our patient could not administer prednisolone due to the presence of HBV. Therefore, we selected surgical treatment as the first option.

This is the first reported case of AIHA in which surgery was performed for an accompanying HCC. For patients with AIHA, transfusion of washed blood cells is desirable. However, irrespective of the type of transfusion performed, hemolysis occurs. Therefore, in this case, blood transfusion was given only once.

Although splenectomy has been performed for many patients with AIHA, surgery for tumors complicating AIHA has been reported for only two patients with renal cell carcinoma[25], and 19 patients with benign ovarian cysts[26,27]. In the case of renal cell carcinoma complicated by AIHA, prompt resolution of AIHA occurred after surgical excision. In 17 of the 19 cases of benign ovarian cyst, the AIHA also improved after surgical excision. For AIHA complicated by dermoid cyst, steroid treatment may sometimes be slightly effective. There is one case report of a Japanese patient who underwent transcatheter

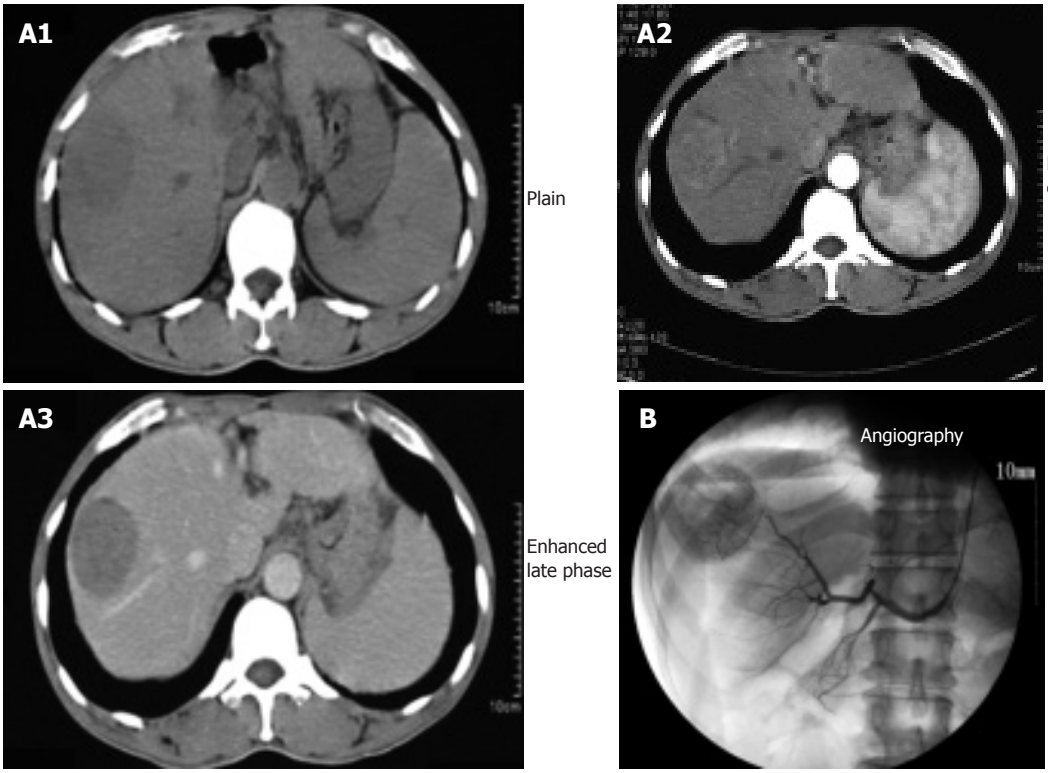

Figure 1 Helical dynamic abdominal CT revealing a liver tumor with a maximum diameter of 5.2 cm in segment 8 (**A**) and abdominal angiography showing hypervascularity in it (**B**).

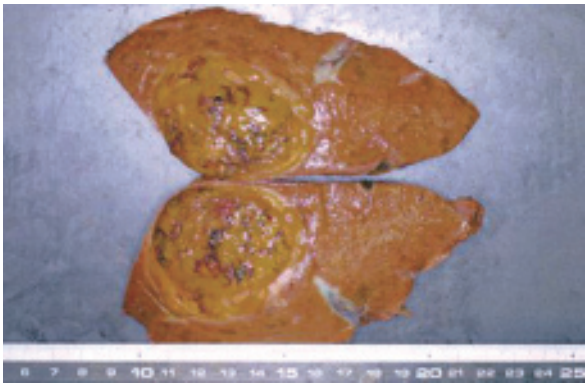

Figure 2 Gross appearance of resected specimen. The cut surface of the resected liver specimen (S8) showed an encapsulated yellow-brownish tumor measuring 52 mm × 40 mm and 250 g.

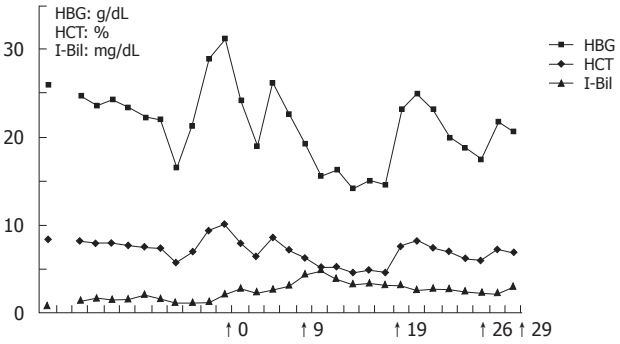

Figure 3 Postoperative course. ↑0: Operation, ↑9:Fever up, ↑19: Sleep out, ↑26: Blood transfusion of washed blood cells, ↑29: Discharged and started intake of lamivudine.

hepatic arterial embolizaion for recurrence of HCC after the partial liver resection, and developed the symptoms of AIHA after this treatment (Table 2)[8]. It is thus unprecedented for liver resection to be performed for a patient with AIHA. In our patient also, anemia improved after surgical excision without treatment of AIHA. In the cases of ovarian tumor mentioned above, AIHA might be regarded as a concomitant symptom of dermoid cyst, i.e. a para-neoplastic syndrome. In our patient, however, we were unable to clearly demonstrate whether AIHA was a para-neoplastic syndrome due to HCC.

Our patient is now being followed up on an outpatient basis, and shows no signs of hepatitis virus, HCC recurrence or symptoms of anemia. This is the first report of safe and successful resection of a complicating liver tumor in a patient with AIHA.

Table 2 Cases of AIHA complications

Complicated disease	Number of complications by AIHA
A-type hepatitis	1
B-type hepatitis	2
C-type hepatitis	11
Autoimmune hepatitis	14
CMV hepatitis	1
Renal cell carcinoma	1[a]
Benign ovarian tumor	19[b]
HCC	2[c]

In patients with renal cell carcinoma (a) and ovarian tumor (b), AIHA improved after resection of them. In two cases of HCC complicated by AIHA (c), one is our case and the other is a case that revealed the symptom of AIHA after TAE for HCC.

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