Nagoya J. Med. Sci. **57.** 153 ~ 157, 1994

BIOCHEMICAL IMPROVEMENT OF CHRONIC HEPATITIS C AFTER GASTROINTESTINAL BLEEDING

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ABSTRACT

Although chronic hepatitis C is frequently complicated by iron overload, it remains unclear whether iron cytotoxicity is involved in the disease process. Five patients with chronic hepatitis C showed rapid reduction of serum aminotransferase activity after gastrointestinal bleeding. Posthemorrhagic reduction of liver enzyme levels lasted for more than one week. Anemia was associated with a reduction of serum ferritin concentration. Considering the short half-lives of circulating liver enzymes, reduced release of enzymes, that is inactivation of cell lysis, is the likely cause of the improved biochemical indices. Reactive iron, which is cytotoxic for patients infected by HCV, may be rapidly incorporated into hemoglobin when erythropoiesis is stimulated. Our observation also suggests that intensive iron removal by phlebotomy is a safe, economic treatment for patients with chronic hepatitis C.

Key Words: Iron, Cytotoxicity, Phlebotomy

INTRODUCTION

Chronic hepatitis C (CHC) is a refractory liver disease. There is evidence that iron accumulation occurs in chronic hepatitis,[1,2] but it is uncertain whether iron hepatotoxicity occurs in patients with CHC.[3,4] Judging from the effect of phlebotomy,[5–7] iron toxicity may contribute to hepatic injury in patients infected with hepatitis C virus (HCV). Establishment of the concept of iron toxicity in CHC is important, because cytotoxic iron, if present, can easily be removed by phlebotomy. Follow-up measurements of biochemical parameters in patients who have experienced massive gastrointestinal bleeding could provide evidence of iron cytotoxicity and serve as a guide for iron removal treatment in CHC.

PATIENTS AND THEIR CLINICAL COURSES

Clinical features of five patients (two women and three men) are summarized in Table 1. Their ages ranged from 53 to 71 years. All patients were positive for antibody to hepatitis C virus (anti-HCV) by second generation assay system (Dainabot, Tokyo) and were being medically treated for chronic liver diseases. Massive gastrointestinal bleeding resulted in severe

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Accepted for Publication in August 30, 1994

Table 1. Clinical Features of Patients

Patient	Age (yrs)	Gender	Diagnosis	Gastrointestinal Bleeding	Transfusion
1	56	femal	CAH	gastritis	no
2	57	male	LC $\underline{c}$ CAH	esophageal varices	yes
3	71	female	CIH	anal fissure	yes
4	53	male	LC $\underline{c}$ CAH	esophageal varices	no
5	58	male	cirrhosis	duodenal ulcer	no

CAH, chronic active hepatitis; LC $\underline{c}$ CAH, cirrhosis with chronic active hepatitis; CIH, chronic inactive hepatitis.

anemia, and four patients required hospitalization. Several units of blood were transfused in two patients who developed hypovolemic shock.

The first patient was a 56-year-old woman with chronic liver disease and hypertension. She had no history of major surgery, blood transfusion, or alcohol abuse. Histologic examination of the liver revealed chronic active hepatitis without histochemical iron deposits. Treatment with azathioprine, 50 mg, and ursodeoxycholic acid, 900 mg daily, was not sufficient to stabilize serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In the meantime, serum enzyme levels declined as mild anemia developed. Fecal test for human hemoglobin was positive. An upper gastrointestinal tract roentgenographic series and colonoscopy did not reveal open ulcer or malignancy. Anemia persisted for the next six months without serious sequelae. Results of a second liver biopsy were the same as those of the previous study.

The second patient was a 57-year-old man admitted to Gamagōri City Hospital because of esophageal bleeding. He was a beer drinker with a history of blood transfusions for massive bleeding from a gastric ulcer. Liver biopsy specimens 10 months before the patient was admitted showed cirrhosis associated with chronic active hepatitis. Histochemical examination results did not show iron in the liver. The patient was treated with transfusions of concentrated red blood cells and endoscopic sclerotherapy for active bleeding from esophageal varices. Bleeding was completely stopped after another two courses of sclerotherapy. He was discharged one month later.

The third patient was a 71-year-old woman with massive bleeding from an anal fissure during hospitalization for chronic hepatitis and osteoporosis. She had no history of alcoholism or blood transfusion. Results of histologic examination one year before the bleeding episode showed chronic inactive hepatitis without histochemical iron deposits. The patient received multiple transfusions of concentrated red blood cells, and recovered from shock after 24 hours. Eight months later she was discharged without serious sequelae.

The fourth patient was a 53-year-old man with cirrhosis associated with chronic active hepatitis. His clinical course is shown in Fig. 1. Results of endoscopic examination showed esophageal varices with red color signs which were treated by endoscopic variceal ligation. A few hours after treatment, active bleeding occurred from the esophageal mucosa distal to the ligated lesions. Massive bleeding was effectively treated without blood transfusion. The patient received iron supplements for one week and was discharged one month later.

The fifth patient was a 58-year-old man with cirrhosis who was admitted to Inazawa City Hospital because of massive gastrointestinal bleeding. He had a history of thoracoplasty for tuberculosis and blood transfusions at the age of 20 years. Results of emergency endoscopy showed active bleeding from a duodenal ulcer and the presence of *Helicobactor pylori* infection.

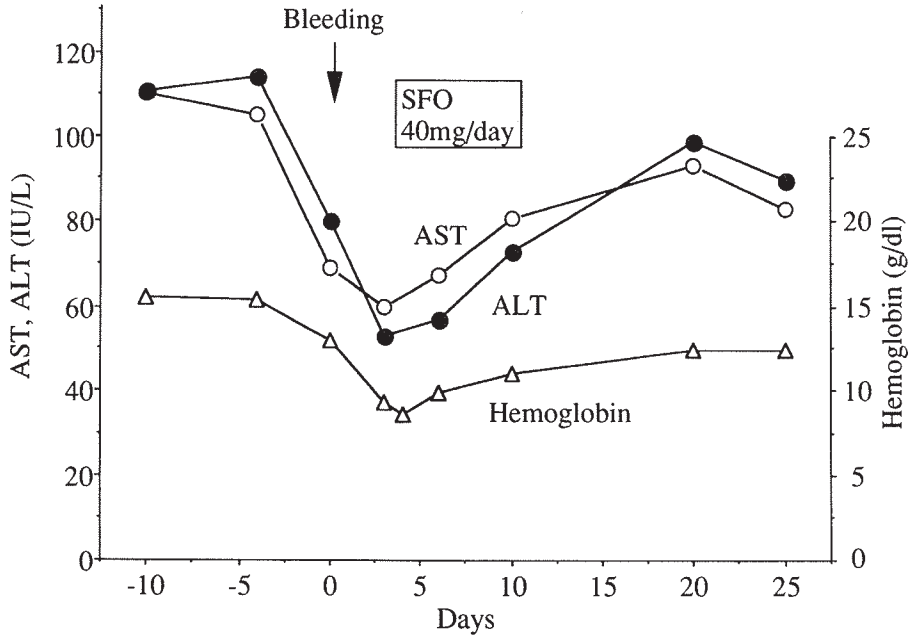

Fig. 1. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were reduced immediately after bleeding and remained low for more than 1 week. SFO, Saccharated ferric oxide.

Combined treatment with clarithromycin and lansoprazole was given during a one-month period of hospitalization. Posthemorrhagic anemia improved without blood transfusion or iron supplements.

LABORATORY TESTS

One of the characteristic findings of blood biochemical tests after gastrointestinal bleeding was anemia, despite blood transfusions (Table 2). Hemoglobin concentrations remained below the baseline one month after the bleeding episodes. Serum levels of ALT were also reduced immediately after the episodes and remained low for more than one week in all patients (Table 3). The AST levels showed changes similar to those of the ALT levels. Serum levels of ferritin, iron

Table 2. Hemoglobin Concentrations (g/dl)

	Hemoglobin Concentrations (g/dl)		
Patient	Before bleeding	One week after bleeding	One month after bleeding
1	12.2	10.7	10.8
2	12.0	10.2	11.5
3	10.0	9.2	9.3
4	15.4	9.3	12.4
5	13.9	8.1	12.4

Table 3. Serum Levels of Alanine Aminotransferase (IU/L)

Patient	Serum Levels of Alanine Aminotransferase (IU/L)		
	Before bleeding	One week after bleeding	One month after bleeding
1	118	79	42
2	91	58	93
3	134	58	26
4	114	53	90
5	64	25	32

Table 4. Serum Levels of Iron Indices

Patient	Serum Levels of Iron Indices						
	Before bleeding			After bleeding			
	Ferritin (μg/L)	Fe (μg/dl)	TIBC (μg/dl)	Ferritin (μg/L)	Fe (μg/dl)	TIBC (μg/dl)	
1	36	71	481	12	44	nd	(one month later)
2	92	135	336	14	90	395	(seven months later)
3	131	110	290	60	94	317	(two months later)

TIBC, total iron binding capacity

nd, no determination

and total iron binding capacity were measured in pairs of pre- and posthemorrhagic sera from three patients using standard laboratory methods. Persistent anemia was associated with a reduction of ferritin concentration (Table 4). Iron indices did not support a diagnosis of hereditary hemochromatosis. Posthemorrhagic ferritin concentrations were normal in the other two patients. Both anti-HCV antibodies and HCV RNA persisted throughout the study.

DISCUSSION

None of our patients had hemochromatosis, but they all had HCV-related chronic liver disorders without overt iron load. Our observation is of interest in terms of cytotoxicity in CHC. Reduction in circulating enzymes might be explained in part by hemodilution after massive bleeding. Considering the short half-lives of circulating liver enzymes, reduced release of enzymes indicating inactivation of hepatocyte necrosis is another likely explanation for the improved biochemical indices. Contribution of HCV may be negligible because repeated phlebotomies in patients affected the serum levels of HCV RNA only slightly.[7]

Hepatotoxic iron may be detoxified in posthemorrhagic anemia. Farinati et al.[3] postulated that HCV damage could be mediated, at least in part, by iron-activated free radical production. Stimulation of hemoglobin synthesis is a physiologic reaction to blood loss. Posthemorrhagic ferritin levels were compatible with a reduced body iron store. Therefore, it is likely that increased incorporation of iron into hemoglobin reduces iron stores, including hepatotoxic iron, after bleeding. The effect of phlebotomy was dependent on pretreatment disease activity rather than

histochemical iron deposits which consisted of aggregated ferritin granules of hemosiderin.[8] Results of an in vitro study showed that the nonlysosomal iron compartment is more cytotoxic than lysosomal iron.[9] Cytotoxic iron may be a nonlysosomal, reactive compartment used during hemoglobin synthesis when erythropoiesis is stimulated. Thus, we postulate that reactive iron, which is cytotoxic for patients infected by HCV, can be depleted by iron removal, either by bleeding or by phlebotomy. Patients who respond poorly to interferon could be treated by intensive iron removal and a second course of interferon.[7,10]

The results of this follow-up study of gastrointestinal bleeding not only suggest the presence of iron cytotoxicity in patients with CHC but also indicate the need for phlebotomy treatment in patients without overt iron load. Bleeding episodes from peptic ulcers or esophageal varices are prevalent in patients with CHC, so our observations may be confirmed by other studies involving a larger number of patients.

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