Acquired Factor VIII Inhibitor in a Non-Hemophilic Patient with Chronic Hepatitis C Viral Infection

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Production of coagulation factor VIII inhibitor is rarely encountered in non-hemophilic patients. A 63-year-old Japanese male suffered from severe bleeding tendency caused by this inhibitor. Although he did not have malignancy or collagen disease, he had chronic hepatitis C virus (HCV) infection. Although HCV is known to induce production of various autoimmune antibodies, this may be the first report of a case with both acquired factor VIII inhibitor and HCV infection.

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Introduction

Coagulation factor VIII inhibitor is often produced in hemophilic patients who frequently receive transfusion of this factor. However, this inhibitor is rarely found in non-hemophilic patients. In the reviews of the non-hemophilic patients with the inhibitor, some cases were shown to have underlying disorders (postpartum, malignancy or collagen diseases), which may have induced immunological disorders and autoimmune antibodies (1, 2). In contrast, the majority of the patients with the inhibitor had no apparent underlying diseases and were then considered to be “idiopathic”. On the other hand, hepatitis C virus (HCV) infection is known to be associated with various immunological disorders or autoimmune antibodies (3). Green and Lechner reported two cases with factor VIII inhibitor who had hepatitis, but the etiology of the liver dysfunction was not described (1). We treated a non-hemophilic patient with factor VIII inhibitor and HCV antibody. This may be the first report of such a case presenting both antibodies.

Case Report

A 63-year-old Japanese male was admitted to our department because of a severe bleeding tendency. He had a history of atherosclerotic occlusions in bilateral femoral arteries and angina pectoris. At the age of 57, he was initially diagnosed to have chronic hepatitis; his prothrombin time (PT) was low nor-

mal (70% of the control value) and his activated partial thromboplastin time (APTT) was slightly prolonged (38.8–40.1 second). One month before admission, hematoma appeared in his oral cavity, and purpura on the left side of his neck. Five days after the onset, hematoma appeared also in his right groin area. Laboratory data showed almost normal PT (PT-INR 1.26), prolonged APTT (55.4 second) and severe anemia (hemoglobin 6.0 g/dl). After anti-platelet agents were discontinued, anemia improved gradually (hemoglobin 11.0 g/dl). However, at one month after the onset of hemorrhagic episodes, he suddenly experienced severe lumbar-back pain. As the pain became worse, he visited the emergency unit of our hospital. At the visit, he showed hypotension (70 mmHg) and severe anemia (hemoglobin 6.3 g/dl). Hematoma was detected in his retroperitoneal area by ultrasonography as well as computed tomography. Under the diagnosis of hypovolemic shock caused by retroperitoneal hemorrhage, he was admitted to our department.

On admission, physical examination revealed old purpurae on his neck and right femoral region, anemic conjunctivae, palmar erythema and clubbed fingers. Laboratory data showed severe normocytic, normochromic anemia (Table 1). Neither rheumatoid factor nor antinuclear antibody was detected, although C-reactive protein (CRP) value was increased. He was positive for HCV antibody, with a viral titer of $10^{5.5}$ copies/50 μ l by competitive RT-PCR. The subtype of his HCV was classified as 1b. Coagulation tests showed mildly prolonged PT (INR 1.47)

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Table 1. Laboratory Data on Admission

Blood cell count:		Blood Chemistry	
White blood cell	13.7×10 ³ /μl	Total protein	7.7 g/dl
Red blood cell	190×10 ⁴ /μl	Albumin	3.8 g/dl
Hemoglobin	6.3g/dl	AST	18 IU/l
Hematocrit	19.7%	ALT	16 IU/l
Reticulocyte	33‰	Lactate dehydrogenase	141 IU/l
Platelet	21.2×10 ⁴ /μl	Alkaline phosphatase	147 IU/l
Serological:		Total bilirubin	0.9 mg/dl
C-reactive protein	2.0 mg/dl	Blood urea nitrogen	23 mg/dl
Hepatitis C virus-Ab	(3+)	Creatinine	1.7 mg/dl
Hepatitis C virus-RNA	10 ^{5.5} copies/50μl, subtype 1b	Na	137 mEq/l
HBsAg	(-)	K	5.5 mEq/l
Urinalysis:		Cl	104 mEq/l
SG	1.030	Glucose	231 mg/dl
pH	5.0	Coagulation factor activities	
Pro	(1+)	II	69% (62-127)
Glu	(+ -)	V	85% (50-150)
OB	(+ -)	VII	49% (65-135)
Coagulation test (normal ranges):		VIII	7% (50-150)
Prothrombin time	14.3 sec	IX	102% (60-140)
PT-INR	1.47 (0.951-1.15)	X	66% (56-138)
APTT	56.9 sec (27-37)	XI	48% (65-135)
Fibrinogen	205 mg/dl (210-310)	XII	142% (50-150)
Factor VIII inhibitor	12 Bethesda units/ml	XIII	56% (70-140)
Factor IX inhibitor	(-)	vWF*	232% (60-170)
AT-III	75% (77.6-123.1)		

HBsAg: hepatitis B virus surface antigen, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, *vWF: von Willebrand factor.

Figure 1. Clinical course after admission. APTT: activated partial thromboplastin time measured with soybean-derived cephalin (DADE FS®, Dade International Inc., Miami, FL, USA), Inhibitor: factor VIII inhibitor, BU: Bethesda units, PT: prothrombin time.

and prolonged APTT (56.9 second) (Table 1). The level of plasma fibrinogen was low (205 mg/dl), whereas that of fibrinogen degradation product (FDP) remained normal (1.5 µg/ml). His clinical course after admission is illustrated in Fig. 1. Briefly, repeated blood transfusion transiently improved his anemia and hypotension, but fresh frozen plasma transfusion failed to control the bleeding tendency itself. He experienced repetitive severe hemorrhagic episodes, including right hemothorax, intramuscular bleeding in his right biceps, macrohematuria, subcutaneous bleeding on the left side of his abdominal wall and bloody stool. On the 10th hospital day, a marked decrease in the activity of coagulation factor VIII (7% of the control) was found and the concentration of factor VIII inhibitor was elevated to 12 Bethesda units/ml (Table 1). The activities of some of the other coagulation factors (II, VII, X, XI, XII) were also slightly decreased or at lower normal ranges, presumably because of liver dysfunction. According to these data, we suspected that his bleeding tendency was mainly caused by the acquired factor VIII inhibitor. Thus, we started steroid pulse therapy using methylprednisolone 1 g/day for 3 days to correct his coagulation abnormalities. Unfortunately, the effect of this therapy was insufficient as his APTT was shortened only from 74.6 second to 65.4 second. Subsequently, we performed plasmapheresis on the 14th hospital day and his APTT value was significantly abbreviated to 53.9 second. As the oozing from the site of catheter insertion was not well controlled, we repeated this procedure twice on the 16th and 19th hospital days. His APTT further improved to 40.9 second, but the oozing from the catheter site continued. This situation led us to perform a second steroid pulse therapy on the 22nd hospital day. On the evening of the day of the steroid therapy, when his APTT value was 47.8 second, severe upper abdominal pain occurred suddenly. As his abdomen was distended with no bowel sound, paralytic subileus was suspected. Hematoma was not detected with ultrasonography, and there was no change in his hemoglobin level (9.0 g/dl). His condition rapidly deteriorated despite supportive therapies, and he died of multiple organ failure on the following day. The level of factor VIII inhibitor remained high (9 Bethesda units/ml) on the day of the second steroid pulse therapy.

Autopsy revealed multiple old hematomae, as detected before his death, and liver cirrhosis of the mesonodular type. Ischemic necrosis of the ileum (length of 50 cm) was found, and his superior mesenteric artery was compressed by massive retroperitoneal hematoma. Microthrombi, which are specific for disseminated intravascular coagulation, were not detected.

Discussion

Production of factor VIII inhibitor is seldom seen in non-hemophilic patients. The mechanism of the acquired factor VIII inhibitor production has not yet been clarified in non-hemophilic patients. Some underlying pathophysiological states, including collagen and autoimmune diseases, pregnancy, and malignancy, have been reported, and these conditions are known to induce immunological disorders and autoimmune antibodies.

In contrast, about half of the patients with the acquired factor VIII inhibitor were considered as idiopathic (1, 2). The present patient did not have major underlying disorders, except for liver dysfunction caused by HCV infection. We diagnosed his liver dysfunction as chronic hepatitis C before his death because of his history of mild elevation of transaminases for more than 6 months, but pathological examination revealed typical cirrhotic changes in his liver. Earlier reports demonstrated that a few of patients with factor VIII inhibitor had hepatic diseases (1, 4, 5). Green and Lechner showed that two patients were associated with hepatitis out of 215 cases with the inhibitor, but the etiology or severity of their chronic liver disease was not evaluated (1). Uoshima et al reported a 61-year-old Japanese male with non-B liver cirrhosis and esophageal varices, who suffered from gingival bleeding and subcutaneous hematoma caused by factor VIII inhibitor (4). On admission, his antinuclear antibody, thyroid test and microsome test were positive, but they became negative along with the recovery of his coagulation function due to steroid and immunosuppressive therapies. Neilson et al reported that a non-hemophilic male with the factor VIII inhibitor was associated with non-B non-C liver cirrhosis and hepatocellular carcinoma (5). His titer of the inhibitor was very high (435 Bethesda units/ml) and he died of hepatic failure. In spite of these earlier reports concerning the association of the factor VIII inhibitor and liver diseases, there has been no report of a non-hemophilic patient demonstrating both the factor VIII inhibitor and HCV antibody.

HCV has been reported to be associated with various immunological disorders (3). It is well known that some types of cryoglobulinemia are related to HCV infection (6), and glomerulonephritis without cryoglobulinemia has also been reported to be accompanied with HCV infection (7). In addition, a high prevalence of rheumatoid factor was reported in HCV-positive patients (8), although its immunological role is not yet well understood. On the other hand, many patients with chronic hepatitis C have sialoadenitis like sicca syndrome (9). Furthermore, liver/kidney microsomal (LKM) autoantibody, one of the specific markers of autoimmune hepatitis (type II), has often been detected in HCV RNA-positive patients without autoimmune hepatitis (10). Other autoantibodies, including anti-GOR, smooth muscle antibody and antinuclear antibody, are also reported to be more frequently detected in HCV-positive patients than in HCV-negative patients (11).

The combination of the therapeutic measures usually induces disappearance of the factor VIII inhibitor or control of bleeding tendency in patients with the acquired inhibitor. In contrast, despite plasmapheresis and steroid pulse therapy, the levels of factor VIII inhibitor remained high and the bleeding tendency was not completely controlled in the present case. At autopsy, his superior mesenteric artery was compressed by a massive retroperitoneal hematoma, and this compression was suspected to be responsible for the ischemic necrosis of the ileum. These pathologic findings also suggest that the control of coagulation abnormalities attained in this patient was insufficient for complete prevention of fatal bleeding episodes.

Production of the coagulation factor VIII inhibitor and HCV

infection are known as serious complications of blood transfusion therapy to patients with congenital hemophilia A (12). In contrast, the association of the factor VIII inhibitor and HCV antibody in non-hemophilic patients is not well recognized and its molecular mechanisms remain to be elucidated. As discussed earlier, the changes in immunological systems induced by HCV infection may be responsible for the inhibitor production, although there is no direct evidence of immunological crossover between the factor VIII inhibitor and HCV antibody.

We reported a non-hemophilic case demonstrating both factor VIII inhibitor production and HCV infection. Although the direct relationship between these two events remains to be elucidated, it may be possible that this inhibitor was produced as a result of the immunological disturbances evoked by HCV infection.

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