CASE REPORT

Acquired factor V deficiency following transcatheter arterial chemoembolization for hepatocellular carcinoma: a case report

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Abstract Acquired factor V deficiency is a rare condition associated with a wide variety of causes. We herein report the case of a 75-year-old man who developed acquired factor V deficiency associated with gastrointestinal bleeding after transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma. Laboratory data revealed prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) and a significant reduction in the factor V (FV) activity. Infusion of fresh-frozen plasma (FFP) was unable to correct the prolonged PT and APTT. Four weeks after onset, his coagulation parameters improved spontaneously with no particular treatment. The patient developed acquired FV deficiency after TACE treatment using cisplatin, and thus, cisplatin was suspected as the cause of this coagulopathy. If coagulopathy that is not corrected by FFP transfusion after TACE is observed, acquired factor V deficiency, although extremely rare, should be considered.

Keywords Acquired factor V deficiency · Transcatheter arterial chemoembolization · Hepatocellular carcinoma

Introduction

Factor V (FV) is a cofactor for Factor Xa (FXa) in the formation of the prothrombinase complex, accelerating the conversion of prothrombin to thrombin [1, 2]. FV inhibitors are antibodies that bind to FV and either promote its degradation or prevent it from functioning in coagulation [3].

Inhibitors directed against FV occur rarely and may appear at any age, and the clinical symptoms vary greatly [4]. Indeed, the clinical phenotype of patients with acquired FV inhibitors might span from asymptomatic laboratory abnormalities to life-threatening bleeding [4]. Acquired FV inhibitors have been reported to be associated with the presence of several relative risk factors, including bovine thrombin administered during surgical procedures, antibiotic administration (especially the lactam group), blood transfusions, cancers, infections, and autoimmune disorders [5]. However, it is difficult to prove the reason or their relationship in many cases.

We herein report a rare case of a patient with an acquired FV deficiency who presented with gastrointestinal bleeding following transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).

Case report

A 71-year-old man with a history of chronic hepatitis C was referred to our hospital because of a liver tumor detected by routine liver ultrasonography. Abdominal enhanced computed tomography (CT) showed a 7.0-cm mass in the posterior section of the liver surrounded by many intrahepatic metastases with arterial phase enhancement followed by a washout in the portal phase (Fig. 1a, b). The serum levels of α -fetoprotein (AFP), lens culinaris agglutinin-reactive

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Fig. 1 Abdominal enhanced computed tomography prior to transcatheter arterial chemoembolization. There was a 7.0-cm mass in the posterior section (arrows) surrounded by many intrahepatic metastases (arrow head). **a** Arterial phase; **b** portal phase. **c** angiography of the patient during transcatheter arterial chemoembolization. There was a large hypervascular tumor at the right lobe of the liver supplied by the right hepatic artery (arrows). **d** Abdominal enhanced computed tomography after transcatheter arterial chemoembolization. Lipiodol remained in the tumor of the right liver lobe (arrows)

AFP isoform (AFP-L3), and des- γ -carboxy prothrombin (DCP) were 519.8 ng/mL (normal range, <20 ng/mL), 11.0% (normal range, <10%), and 185 mAU/mL (normal range, <40 mAU/mL), respectively. Based on the typical imaging features and elevated tumor markers, the liver tumor was diagnosed as HCC.

The results of laboratory investigations are shown in Table 1. The proteins related to blood coagulation and the fibrinolytic system showed no abnormalities before treatment.

The indocyanine green retention rate at 15 min (ICG-R15) was 14.7%, and the ICG fractional disappearance rate (K-ICG) was 0.128.

We initially planned to perform radical resection of the liver tumor and suggested right hepatectomy. Portal vein embolization (PVE) of the right liver was performed to induce hypertrophy in the left lobe, because the future liver remnant (FLR) volume was not sufficient (liver resection rate: 62%). After PVE, the liver function was not impaired (ICG-R15: 13.0%), and coagulopathy was not observed. However, the FLR was not sufficiently enlarged at 1 month later (liver resection rate: 41%). Therefore, we decided to treat the patient with TACE and wait for sufficient enlargement of the FLR. The patient underwent TACE treatment

with cisplatin (Iacall®; 80 mg) and super-liquid iodized oil (Lipiodol®; 8 ml) via the right hepatic artery (Fig. 1c, d).

The changes in the laboratory data indicating liver damage, inflammatory response, and blood coagulation and regarding the fibrinolytic system are shown in Table 1. At 9 days after TACE, laboratory examinations showed a prolonged PT of 24.8 s and APTT of 72.4 s, while the HPT was normal (87%), as shown in Table 1. At 10 days after TACE, the patient experienced melena, and emergency upper gastrointestinal endoscopy was performed. It showed multiple ulcers in the duodenum (Fig. 2). Because there were no evident active bleeding or visible vessels at the point, endoscopic hemostasis was not required, and a proton pump inhibitor was prescribed. With the specific etiology unknown, the patient received a transfusion of fresh-frozen plasma (FFP) and vitamin K for 5 days. However, his prolonged PT and APTT persisted.

Despite the prolonged PT and APTT, his HPT remained normal, and the PT and APTT were not corrected on mixing with normal plasma (Fig. 3), suggesting the presence of an inhibitor of some kind of coagulation factor. At 15 days after TACE, assays for various coagulation factors were performed, and the factor V level was found to be markedly decreased to 4% (normal range 70–135%), whereas the values of other coagulation factors were within the normal ranges (factor II, 50%; factor VII, 57%; factor VIII, 94%; factor IX, 87%; factor X, 98%; factor XI, 68%; factor XII, 71%). These results indicated the presence of antibodies against factor V and suggested a diagnosis of acquired factor V deficiency.

Although the use of corticosteroids was considered, the PT and APTT shortened spontaneously, and there were no bleeding events after the gastrointestinal bleeding. At 26 days after TACE, the factor V level increased to 46%, and at 37 days, it increased to 116% spontaneously. The patient, therefore, did not receive corticosteroids or other immunosuppressive treatments (Fig. 4).

Ultimately, the patient did not undergo surgical treatment because of concerns of difficulty achieving hemostasis during surgery. The patient has repeatedly received TACE using epirubicin, as cisplatin was suspected of causing his acquired factor V deficiency, and he is still alive at present, more than 4 years later, without any coagulopathy.

Discussion

FV inhibitors are the second most frequent inhibitors, next to factor VIII inhibitors [6]. Factor VIII inhibitors are well known for their association with acquired hemophilia A, a potentially life-threatening hemorrhagic disorder caused by the development of autoantibodies directed against coagulation factor VIII [6].

Table 1 Changes in the laboratory data before and after treatment

	Before PVE	1 day after PVE	7 day after PVE	1 day after TACE	10 day after TACE	15 day after TACE	26 day after TACE	37 day after TACE
White blood cell count (μL)	5800	6600	3300	5200	7200	5200	3200	4100
Platelet count ($\times 10^3/\text{mL}$)	14.2	12.4	13.7	11.4	17.3	23.7	23.1	14.8
C-reactive protein (mg/dL)	0.05	0.54	0.05	0.03	5.35	2.61	0.25	
Aspartate aminotransferase (U/L)	68	180	39	187	49	51	58	
Alanine aminotransferase (U/L)	76	136	43	90	37	30	42	
Total bilirubin (mg/dL)	1	1.2	0.9	1	0.8	0.8	0.8	
Albumin (g/dL)	4.7	3.5	3.6	3.5	2.5	3.2	3.7	
Prothrombin time (sec)	11.6	12	11.7	12.5	28.6	29.8	16.1	12.9
Activated partial thromboplastin time (s)	32.6	29.6	31.8	30.2	98	108.6	42.7	35.6
Fibrinogen	339	348			636	580		
Hepaplastin test (%)	94		78			87	92	97
Protein C (%)	105					65		
Antithrombin III (%)	126	117	118		91	84		
Plasminogen activity (%)	99					92		
$\alpha 2$ plasmin inhibitor (%)	106					107		
Fibrin/fibrinogen degradation products ($\mu\text{g/mL}$)	4.2	18.9	5		7.9	8.1		
D-dimer ($\mu\text{g/mL}$)	<0.5	13.3	2.6		3.5	2.8		
Thrombin-antithrombin complex (ng/mL)	1		1.49			1.24		
Plasmin- $\alpha 2$ plasmin inhibitor complex ($\mu\text{g/mL}$)	0.88					1.62		
Soluble fibrin monomer complex ($\mu\text{g/mL}$)	<3					14.8		
Factor II (%)						50	64	
Factor V (%)						4	46	116
Factor VII (%)						57	80	
Factor VIII (%)						94	98	
Factor IX (%)						87	93	
Factor X (%)						98	101	
Factor XI (%)						68	70	
Factor XII (%)						71	95	

PVE portal vein embolization, TACE transcatheter arterial chemoembolization

Fig. 2 Emergency upper gastrointestinal endoscopy when melena was observed. There were multiple ulcers in the duodenum (a, b). There were no exposed blood vessels or active bleeding

The clinical presentation of factor V inhibitors can range from asymptomatic laboratory abnormalities to life-threatening bleeding [4]. If bleeding occurs, it predominantly involves the mucous membranes of the gastrointestinal system, airway, and urinary tracts [7]. Although intracranial hemorrhaging is rare, once it occurs, the mortality rate reaches up to 50%. Acquired factor V deficiency due to FV inhibitors has been associated with a number of conditions, such as bovine thrombin administered during surgical procedures, antibiotic administration (especially the lactam group), blood transfusions, cancers, infections, and autoimmune disorders [5]. The laboratory data in case of the presence of FV inhibitors show reduced acquired V activity and

Fig. 3 Cross-mixing test. The prolonged PT (**a**) and APTT (**b**) were not corrected on mixing with normal plasma. *PT* prothrombin time, *APTT* activated partial thromboplastin time

Fig. 4 PT, APTT, and FV activity during post-TACE treatment. At 10 days after TACE, the patient experienced gastrointestinal bleeding. Four weeks after onset, the PT, APTT, and FV activity improved spontaneously with no particular treatment. *PT* prothrombin time, *APTT* activated partial thromboplastin time, *TACE* transcatheter arterial chemoembolization

prolonged PT and APTT, with no improvement in the mixing test. The inhibitor is confirmed and titrated using the traditional Bethesda method [4]. In the present case, coagulopathy, such as prolonged PT and APTT, was not observed after PVE but was observed after TACE (Table 1). Considering that the same antibiotic (Cefmetazole) was used in both PVE and TACE treatment (although this has been reported to be a possible cause), and cisplatin was suspected of causing this coagulopathy.

However, there is no standard treatment protocol for acquired factor V deficiency due to FV inhibitors. The therapeutic regimen of acquired FV inhibitors consists of

blood component replacement therapy, immunosuppression, high-dose intravenous immunoglobulin, and the use of extracorporeal circulation [3, 7]. Transfusions of FFP or platelet and prothrombin complex concentrates have been used for bleeding patients, but the effects of these treatments have mostly been dismal due to the low concentration of FV [8]. Platelet concentrates can protect FV from inhibitors, thereby producing a satisfactory effect in terms of bleeding control [8].

Immunosuppressive regimens with corticosteroids alone or in association with cyclophosphamide or other immunosuppressants have been used successfully to suppress

autoantibody production in many cases. The anti-CD20 monoclonal antibody rituximab has been reported to be useful with severe and symptomatic patients [5].

In this patient, the prolonged PT and APTT improved spontaneously without the use of corticosteroids or any other specific treatment. The patient was unable to receive surgical treatment due to concerns of difficulty achieving hemostasis during surgery and thus continued to receive TACE treatment by changing cisplatin to epirubicin. Since this coagulopathy, there have been no bleeding events or new instances of prolonged PT and APTT. If coagulopathy that is not corrected by FFP transfusion after TACE is observed, acquired factor V deficiency should be considered as a possible reason for this rare phenomenon.

Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to declare.

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