

Acquired Inhibitors to Multiple Coagulation Factors (V, IX, and XII) Identified in a Unique Patient with Hepatocellular Carcinoma

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Abstract

An acquired formation of inhibitors to coagulation factors is a rare type of coagulopathy. The development of inhibitors for multiple coagulation factors has never been reported. A 75-year-old Japanese female underwent interventional therapy for hepatocellular carcinoma. Five days after the last intervention, her prothrombin time decreased to 10%, and her activated partial thromboplastin time (APTT) lengthened to 265.1 sec. The activities for coagulation factors showed significantly reduced activities (<10%) of factors V, IX, and XII. A cross-mixing test demonstrated an inhibitor pattern, and inhibitory antibodies against factors V, IX, and XII were detected. We discuss our patient's etiology and pathogenesis.

Key words: neutralizing antibody, blood coagulation factors, blood coagulation test, hepatocellular carcinoma, corticosteroids

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Introduction

The development of acquired inhibitors to coagulation factors is a rare coagulopathy, with a prevalence of 1.5 cases among 1 million per year (1). The most commonly observed acquired inhibitor (75-90% of all cases of an acquired inhibitor) is "acquired hemophilia A," in which the production of inhibitor against factor VIII occurs non-genetically (1). The second-most common acquired inhibitor (2-7% of cases) is inhibition to factor V (2). The inhibitor risks are not homogeneous, but some contributing factors have been described in a consensus report on acquired inhibitor cases among hemophilia patients (3). According to that report, no definitive disease condition for acquired inhibitors to coagulation factors has been identified, although pregnancy was noted to contribute to antibody formation. However, some underlying diseases and conditions are common among the reported cases of acquired inhibitors to factors VIII and V, including auto immune diseases (4), surgical procedures (2, 5), exposure to an antibody (6), and malignan-

cies (7). Some of these reports' authors speculated that these underlying conditions might have attenuated the production of the autoantibody for a specific coagulation factor, which is known as an acquired inhibitor.

Acquired inhibitors to a coagulation factor are classified into two types based on the mechanism of antibody creation: one type uses an antibody against an alloantigen supplemented as an external coagulation factor, and the other type uses an autoantibody. We have been unable to find any previous cases in which an acquired inhibitor to multiple coagulation factors was reported.

We herein report a case of a recent patient with inhibitors to multiple coagulation factors and discuss our speculation regarding the pathogenesis.

Case Report

The patient was a 75-year-old Japanese female who had been referred to us due to coagulopathy after treatment for hepatocellular carcinoma (HCC), clinical stage T3N0M0, stage III. She had been diagnosed with non-B non-C HCC

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Table. Coagulation Values and Coagulation Factor (Top) and Laboratory Data (Bottom).

Coagulation		Coagulation factor	(%)
PT	10 %	II	58
PT-INR	7.32	V	2
APTT	265.1 sec	VII	43
Fibrinogen	324 mg/dL	VIII	79
AT III	67 %	IX	6
FDP	4.4 µg/dL	X	49
		XI	43
		XII	5
		XIII	86
CBC		Biochemistry	Biochemistry
WBC	2,400 /µL	CRP	2.42 mg/dL
RBC	237×10 ⁴ /µL	TP	6 g/dL
Hb	10 g/dL	ALB	2.6 g/dL
Hct	31.1 %	BUN	13.1 mg/dL
Plt	7.0×10 ⁴ /µL	Cr	0.64 mg/dL
		UA	4.1 mg/dL
		Na	138 U/L
		K	2.6 U/L
		Cl	97 U/L
		T. BIL	1.2 mg/dL
		GOT	69 U/L
		GPT	52 U/L
		LDH	210 U/L
		ALP	372 U/L
		γ-GTP	45 U/L
		CK	26 U/L
		Amylase	5 U/L
		NH3	86 µg/L

and treated with various local therapies for two years. She underwent repeated interventional therapy including radio-frequency ablation (RFA), transcatheter arterial embolization (TAE), and transcatheter arterial chemo-embolization (TACE). Her liver function was judged as Child-Pugh A, without any coagulation disorder before the onset of this coagulopathy. Five days after the last RFA, her laboratory data revealed significant prolongations of prothrombin time (PT, 10%) and activated partial thromboplastin time (APTT, 265.1 sec) (Table). We analyzed the activities of her whole coagulation factors and found that the activities of factors V, IX, and XII were significantly decreased compared to normal levels (below 10%) (Table). Other coagulation factors were lower than the normal ranges (40-79%), except for factor XIII, and the cause was thought to be the patient's diminished liver function.

A cross-mixing test using normal plasma from a healthy volunteer was performed. After a 2-h incubation at 37°C, the results revealed an inhibitor pattern which indicated that the patient had an inhibitor to multiple coagulation factors. Ultimately, inhibitory antibodies against factors V, IX, and XII were suggested in her serum. No autoimmune antibodies were detected, including antinuclear antibody (ANA), antimitochondrial M2 antibody (AMA), and anti-smooth muscle antibody (SMA). No clinical manifestation implying autoimmune diseases was found, including characteristic skin eruption and arthropathy. Anti-phospholipid antibodies were absent or marginal; lupus anticoagulant (LA) showed a 1.07 ratio (normal range 0-1.3), the anti-cardiolipin (CL) antibody level was 11.2 U/mL (normal range 0-10 U/mL), and the anti-CL-β2 glycoprotein I complex antibody level was 0.7 U/mL (normal range 0-3.5 U/mL).

The coagulation factors' activities were determined by a

Bethesda inhibitors assay (8). The activities of coagulation factors V, IX, and XII were measured independently as 22.4, 1.32 and 1.40 BU, respectively (8). We therefore diagnosed the patient with multiple inhibitors for coagulation factors V, IX, and XII. She was asymptomatic without a bleeding tendency at the diagnosis. Other laboratory findings obtained at the onset of coagulopathy were unremarkable (Table). Immunoglobulin A, G, and M (IgA, IgG, and IgM) were 270, 983, and 72 mg/dL (2 weeks before the onset), 289, 1,747 and 72 mg/dL (at the onset), and 289, 1,141 and 33 mg/dL (at 6 months after the treatment initiation), respectively. The patient's IgG was elevated at the onset of coagulopathy.

Following the diagnosis, we immediately administered immunosuppressive therapy with daily 1.0 mg/kg prednisolone, and the patient's prolonged PT and APTT values responded well. The treatment course and recovery are illustrated in Figure. The PT and APTT returned to within normal ranges within approximately two weeks after the initiation of prednisolone. Throughout the immunosuppressive therapy, no bleeding tendency was observed. The patient was uneventfully discharged on the 29th day after the initiation of prednisolone therapy. Through the first 30 days after the start of the prednisolone treatment, the coagulation activities of factors V, IX, and XII gradually recovered, and all of the inhibitors for factors V, IX and XII became completely undetectable by day 32.

Discussion

Regarding the production mechanism of inhibitors, the simultaneous appearance of various inhibitory antibodies corresponding to multiple antigens is extremely rare. However, the laboratory data of our patient ruled out the possibility

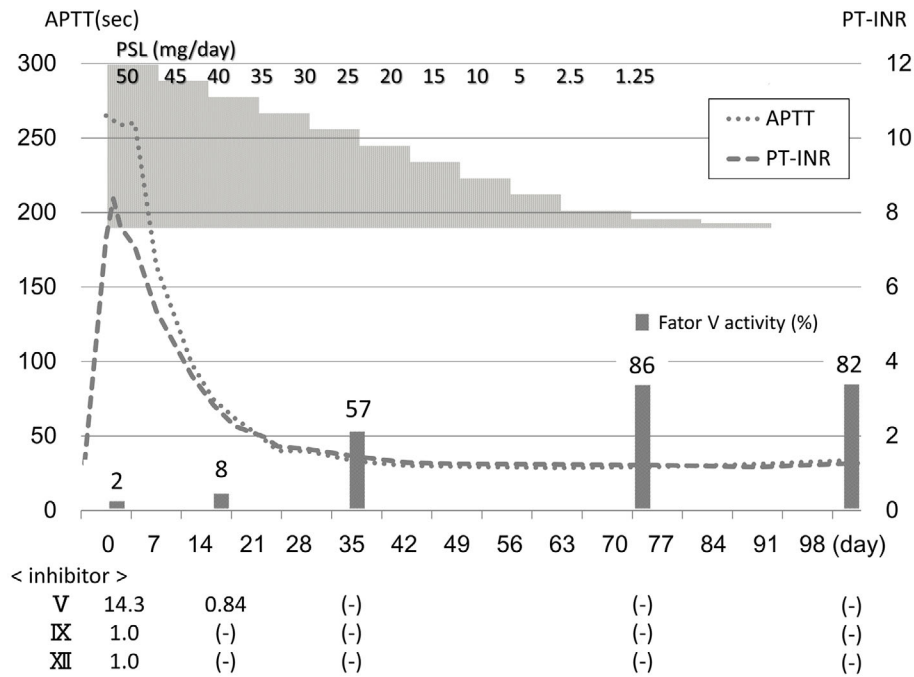


Figure. The patient's coagulopathy recovered following the administration of corticosteroids.

that she harbored immunogenic conditions, which can be associated with antibody formation. The only possible risk factor for the patient's antibody formation appeared to be an intervention for her HCC. The consensus report issued regarding "non-genetic risk factors and the development of inhibitors in hemophilia" (3) addressed a "danger signal" as a crucial concept. This concept describes an invasive stimulus to the body's immune system that can give rise to the production of an alloantibody to external coagulation factors. The danger signal hypothesis (9) originally denoted a universal theoretical mechanism for antibody production promoted by the self-intracellular endogenous molecules as an adjuvant. Henceforth, this model was assumed to cover the production of both alloantibodies and the autoantibodies.

We speculate that, in our patient, an inhibitor antibody had been induced in a previous invasive procedure for her HCC, although we were not able to discern the time point at which this antibody developed. In this patient, the inhibitors manifested just after an intervention procedure for HCC. Barring this possibility, the malignancy itself is the most likely cause, which is well recognized. Although a routine laboratory test for coagulation was not performed, the latest laboratory findings for coagulation before her admission had not revealed any evidence of coagulopathy, such as PT prolongation. The remission of her coagulation disorder and the disappearance of the inhibitors in response to corticosteroid therapy confirm that she had a reversible autoimmune reaction.

An underlying pathophysiology was suggested in a review of acquired inhibitors of factor V (10). Feinstein described a close relationship between acquired inhibitors of factor V and major surgery, noting that factor V might be modified during the hemostasis process and increase the antigenicity.

This would explain why, in this hemostatic process, the coagulation factor could no longer be recognized as self.

We examined the molecular homology and structural homology seen in the three coagulation factors (V, IX, and XII) and found that there was no common region among these three antigens (11). Factor V is an essential protease that acts as a cofactor of factor X, with a molecular weight (MW) of 330,000. Factor V and factor VIII have identical amino acid sequences in their three A domains and two C domains, and they share a similar three-dimensional structure. Factor IX, known as Christmas factor, is a serine protease that activates coagulation factor X, with a MW of 56,000. Factor IX has a structure similar to that of protein C (MW 62,000). Factor XII, known as Hageman factor, has a MW of 80,000 and activates factor XI, participating in the intrinsic coagulation pathway at the starting point. Thus, the three coagulation factors observed in our patient (V, IX, and XII) are all classified as different types of coagulation protein. While we did not observe a common molecular homology among these three factors, this result does not eliminate the possibility that the same epitope might be found among the antigens. Our patient's case is quite special because multiple coagulation factors on different coagulation pathways were involved. The cytokines involved in the malignant process also explain the autoimmune mechanism to multiple coagulation factors in cancers (7).

The clinical presentations of patients with acquired inhibitors to coagulation factors vary, ranging from a lack of apparent clinical bleeding to fatal hemorrhagic events (5). Despite a very low coagulation factor level, spontaneous bleeding did not always occur in the patients in the study of Kessler et al. (8). This is explained by the difference in the inactivation kinetics of coagulation factor by autoantibod-

ies (8). It has been reported that autoantibodies show nonlinear inactivation kinetics, a rapid initial inactivation phase, and a slow equilibrium phase (8). If, as in our present case, an inhibitor can be successfully attenuated by corticosteroid therapy, it is crucial to determine the diagnosis before any serious hemorrhagic events occur. A routine coagulation test can be useful in identifying cases of acquired inhibitor to coagulation factor. We recommend that at-risk patients who undergo multiple invasive interventions (as our patient did) be monitored closely by a routine coagulation test. However, the criteria for identifying such patients are still under discussion.

The authors state that they have no Conflict of Interest (COI).

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Authors' contributions: OI and MU managed the patient's case, contributed to the literature search, and wrote the manuscript. OI also made substantial contributions to the conception and design of this report. MU qualified the patient's data, suggested important intellectual content, and reviewed the manuscript. TA was involved in the drafting and supervision of the manuscript and took part in the critical discussions. All of the authors read and approved the final version of the manuscript.

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