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Running Head: acquired Factor VIII inhibitor

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Abstract

We report a case of successful treatment of acquired factor VIII inhibitor after extensive visceral surgery. A 71-yr-old man who operated for bile duct cancer had active bleeding in the abdominal drainage tube on postoperative day (POD) 5, and prolonged aPTT was detected (83.1s) on POD 7. Extensive coagulation work up revealed Factor VIII deficiency (1%), diagnosis of an acquired Factor VIII deficiency was established when a factor VIII inhibitor of 8 Bethesda units was demonstrated. Patient treated with activated prothrombin complex concentrate (aPCCs) bloody discharge was stopped within three days. Inhibitor elimination was started using prednisolone (PSL) on POD 20, rituximab; was administered on POD 74 and 81. Factor VIII inhibitor was disappeared until POD 124, Factor VIII (72%) and aPTT recovered to 45.9s. This case report could show usefulness of aPCCs and Rituximub in the treatment of acquired hemophilia associated with visceral surgery.

Key words: postoperative hemorrhage, acquired haemophilia, factor VIII inhibitor

INTRODUCTION

Acquired hemophilia A (: AHA) is one of the serious hemorrhagic disorder due to autoantibodies against coagulation factor VIII[1),2)]. However, the incidence of this rare disease is approximately 1.5 cases/million/year, we still don't know much about the mechanism.

In many cases, it developed with a malignancy, autoimmune disease or surgery, and somehow associated with elderly person[1) - 3)]. While unusual postoperative bleeding was detected and an unexplained isolated prolonged aPTT suggest the diagnosis of acquired hemophilia A, and prompt further investigation, is indicated. Fatal bleeding like this disease should be controlled for patient even in perioperative period. Some bypassing agents, such as recombinant activated FVII or activated pro-thrombin complex concentrate[4) - 6)] are the first choice. In addition, subsequent immunosuppressive therapy is necessary for autoantibody eradication. Corticosteroids or combination therapy with cyclophosphamide has been recommended as initial treatment, however, postoperative infection disease and delayed wound healing were difficult complications[7)]. Recently, rituximab, a monoclonal chimeric antibody to the CD 20 antigen, has also shown to be effective to factor VIII inhibitor autoantibody eradication[7) - 9)].

Here, we report a case of successful treatment of acquired factor VIII inhibitor, using bypassing agent and corticosteroids with rituximab, after extensive visceral surgery.

CASE REPORT

A 71-yr-old man presented with jaundice and skin itching without a history of haemophilia or previous bleeding symptom. Computed tomography (CT) and nuclear magnetic resonance imaging (MRI) revealed dilated common bile duct was obstructed at pancreatic portion by tumor (Fig. 1). Rapidly, endoscopic retrograde biliary drainage was performed, and then laboratory data became normal. On 7th day before surgery, acute obstructive cholangitis was occurred due to the drainage tube trouble. Primary drainage tube was removed, and endoscopic nasal biliary drainage tube was inserted to treat cholangitis, for better drainage. He recovered from septic state, but prolonged activated partial thromboplastin time (aPTT: 54.3s) was remained which is predictive parameter of acquired haemophilia (Fig. 2). His past medical history revealed hypertension, angina pectoris, moyamoya disease, diabetes mellitus, and phyothrax. These diseases were well controled, and he was physically active. Therefore, radical pancreaticoduodenectomy was performed for bile duct cancer. Perioperative blood loss was 330ml. Doripenem and micafungin were used for preventive treatment, 0.25mg twice a day and 50 mg once a day, respectively. On postoperative day (POD) 5, active bloody discharge was found from the abdominal drainage tube which was placed around intestinal anastomosis. The amylase level of the drain discharge was 16 IU/l and bacterial culture revealed little amount of candida. Prolonged aPTT was getting worse, 83.1s on POD 7 , erythrocyte concentrate and flesh frozen plasma were transfused for progressive anemia (hemoglobin 6.2 mg/dl). CT scan could not detect bleeding point or pseudoaneurisum. On POD 10, leakage of gastro-jejunosotomy was noticed, bloody discharge still continued. On POD 14, aPTT has reached 126s we consulted hematology staff (Fig. 2). Detailed coagulation work up revealed Factor VIII deficiency (1%),

diagnosis of an acquired Factor VIII deficiency was established when a factor VIII inhibitor of 8 Bethesda units was demonstrated (Table. 1). Patient treated with activated prothrombin complex concentrate (aPCC; FEIBA [Factor VIII bypassing activity], Vienna, Austria) at a dose of 50 units/kg twice daily, thereafter, bloody discharge was stopped within three days. After urgent anti-hemorrhagic treatment, inhibitor elimination was started using prednisolone (PSL 1mg/kg/day) on POD 20. Active bleeding hasn't seen, however, an enterocutaneous fistula had developed at gastro-jejunostomy. To acceralate wound healing PSL was tapered to 0.5mg/kg/day on POD 30. However, aPTT was still prolonged subcutaneous and intramuscular hematoma which produced severe continuous pain, have developed on POD 37. FEIBA was administered at the same dose for three days, and hematomas were disappeared eventually (Fig. 3). On POD 50 central vein catheter was infected and removed immediately, but aPTT elongation was reboosted by this event. As Factor VIII inhibitor elimination therapy, rituximab (375mg/m2), and a monoclonal chimeric antibody to the CD 20 antigen was administered on POD 74. Another rituximab was added on POD 81, from POD 86 PSL was reduced by half for a week, finally stopped on POD 120. Factor VIII inhibitor was disappeared until POD 124, Factor VIII (72%) and aPTT (45.9s) recovered to normal level (Table. 1, Fig. 2). On POD 137 enterocutaneous fistula closed finally, thereafter, oral intake had started, general condition was getting better and better. So, we recommended to him and his family to have another admission of several months in the nearest hospital, and then he moved on POD 187.

DISCUSSION

The mechanism of acquired hemophilia is sometimes multifocal and still uncertain.

Some factors are related to production of the inhibitor autoantibody, systemic autoimmune disease such as RA and SLE but may develop with a drug and a malignancy, the pregnancy or an operation[1) - 3)]. In our case, preoperative cholangitis and some antibiotics might be the first etiology and invasive surgery for cancer might be another. As Kreuter reported a case of acquired haemophilia in a patient with gram-negative urosepsis and bladder cancer, infectious disease might produce acquired inhibitor antibody[10)]. It is very important to make an immediate diagnosis and to start appropriate treatment as soon as possible, but postoperative condition is sometimes complicated. It might be difficult to discriminate between this disease and other coagulopathy such as disseminated intravascular coagulation[11)]. Three important clinical findings for a diagnosis are significantly prolonged aPTTs, decreasing factor VIII activity, and the titer measurement of the factor VIII autoantibody which is the proof of inhibitor existence by the Bethesda method. Once clinical diagnosis of AHA is confirmed before surgery, any operation shouldn't be indicated[8)]. If inhibitor autoantibody is removed appropriately, any operation can be performed safely as usual[9)]. In our case, diagnosis of hemophilia was confirmed after postoperative bleeding, but we could start hematological screening even at the time point of first aPTT rise predictively, and this kind of delay make it sometimes life-threatening. In such a case, primary hemostasis must be first priority. Extremely high titer inhibitor antibody doesn't respond to the factor VIII replacement therapy, activated prothrombin complex concentrates (aPCCs) or recombinant activated FVII (rFVIIa) has to be used for bypassing therapy[4) - -6)]. Actually, approximately 80% of post-operative bleeding caused by inhibitor antibody was controllable with aPCCs or rFVIIa, sometime different responses to therapy might be seen in each patient. Once bleeding episode which is non-responsive to bypassing

therapy was confirmed, we should switch to another agent. In this case, we used aPCCs first because we just had this in our hospital.

Serious adverse effects of these treatments include DVT, myocardial infarction, and cerebral infarction by the clot formation, but the frequency of adverse effect is not so high. Fortunately, our patient didn't have any complication like angina and cerebral infarction. Therefore, primary hemostasis was made successfully. For the next step, autoantibody removal is necessary to restore normal hemostasis condition. Immunosuppressive therapy should be continuing until remission was achieved. Corticosteroids which have been used for treatment of acquired hemophilia for long time, could wipe off autoantibody in one-third of cases in 3-6 weeks by giving 1mg/kg/day. If remission was not achieved by steroids alone, combination therapy with cyclophosphamide should be provided. Seventy percent of remission rate was reported in the literature[7)], combination therapy is recommended as first choice. Recently, antiCD20 antibody (Rituximub) which decrease B cell's activity selectively, was known to be effective for the treatment of the autoimmune disease such as ITP or AIHA that caused by autoantibody. So, it has used as combination therapy with steroids or even mono-therapy[7) - 9)].

Remission rate is high (77%), and it is listed as a recommendation because antibody depression last until complete remission. So far, we could not conclude which is better without any randomized control trial. Infectious diseases is one of the most serious and frequent complications[5)]. The effect of these immunosuppressive drugs to postoperative wound healing is more complicated and unclear. In our case, we successfully reduced antibodys and steroids with Rituximab. Eventually, enterofistura was closed, but it took long time to treat the liver abscess. Considering about wound healing, Rituximab

monotherapy could be one of the choices in the case of surgery-associated acquired haemophilia[12]. However, it is insurance nonrecognition in Japan, so far we had to start with steroids only. It took approximately one and a half months until we get the approval in the Institutional Review Board which was another delay of treatment. There is little number of cases even in the world, then RCT has been difficult to make. This case report could show usefulness of aPCCs and Rituximub in the treatment of acquired hemophilia associated with visceral surgery.

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Conflict of Interest Statement.

The authors declare no conflict of interest in association with this study.

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Figure legends

Fig. 1

CT and MRI showed common bile duct dilatation and obstruction at pancreatic portion.

Fig. 2

Prolonged aPTT was observed after preoperative cholangitis through the postoperative period. Infections and surgical insult may worsen acquired hemophilia. Immunosuppressive treatment was effective, and steroid was tapered with Rituximab.

Fig. 3

Subcutaneous hemorrhage was appeared with severe pain (left panel). After urgent bypassing therapy, these symptoms were vanished (right panel).

Table. 1

Initial diagnosis was established by Factor VIII deficiency (1%), when a factor VIII inhibitor of 8 Bethesda units was demonstrated. Factor VIII inhibitor was disappeared after immunosuppressive therapy, and Factor VIII recovered to normal level.

	Initial diagnosis (before treatment)		Day 50th	
Factor II	61	%		
Factor V	98	%		
Factor VIII	1	%	72	%
Factor VIII inhibitor	8.0	BU/ml	0.00	BU/ml
Factor IX inhibitor	0.00	BU/ml		

Table 1

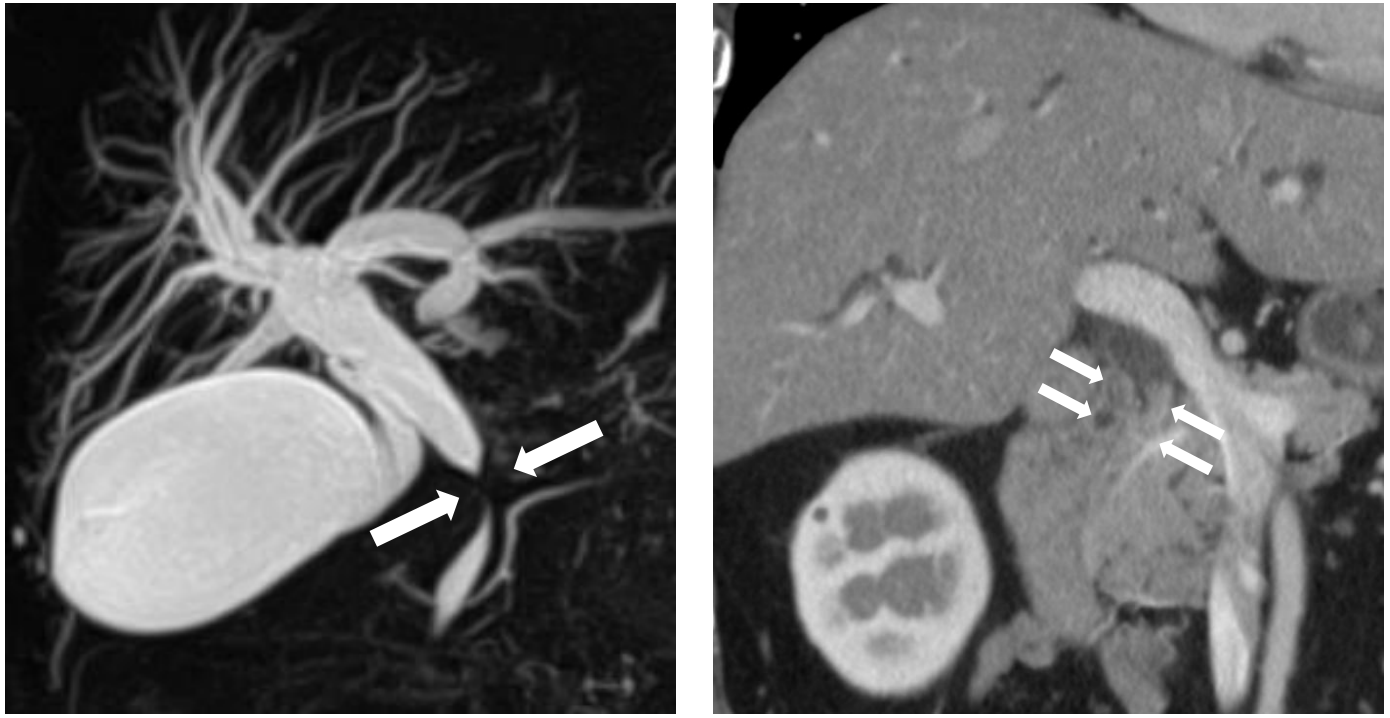

Fig. 1

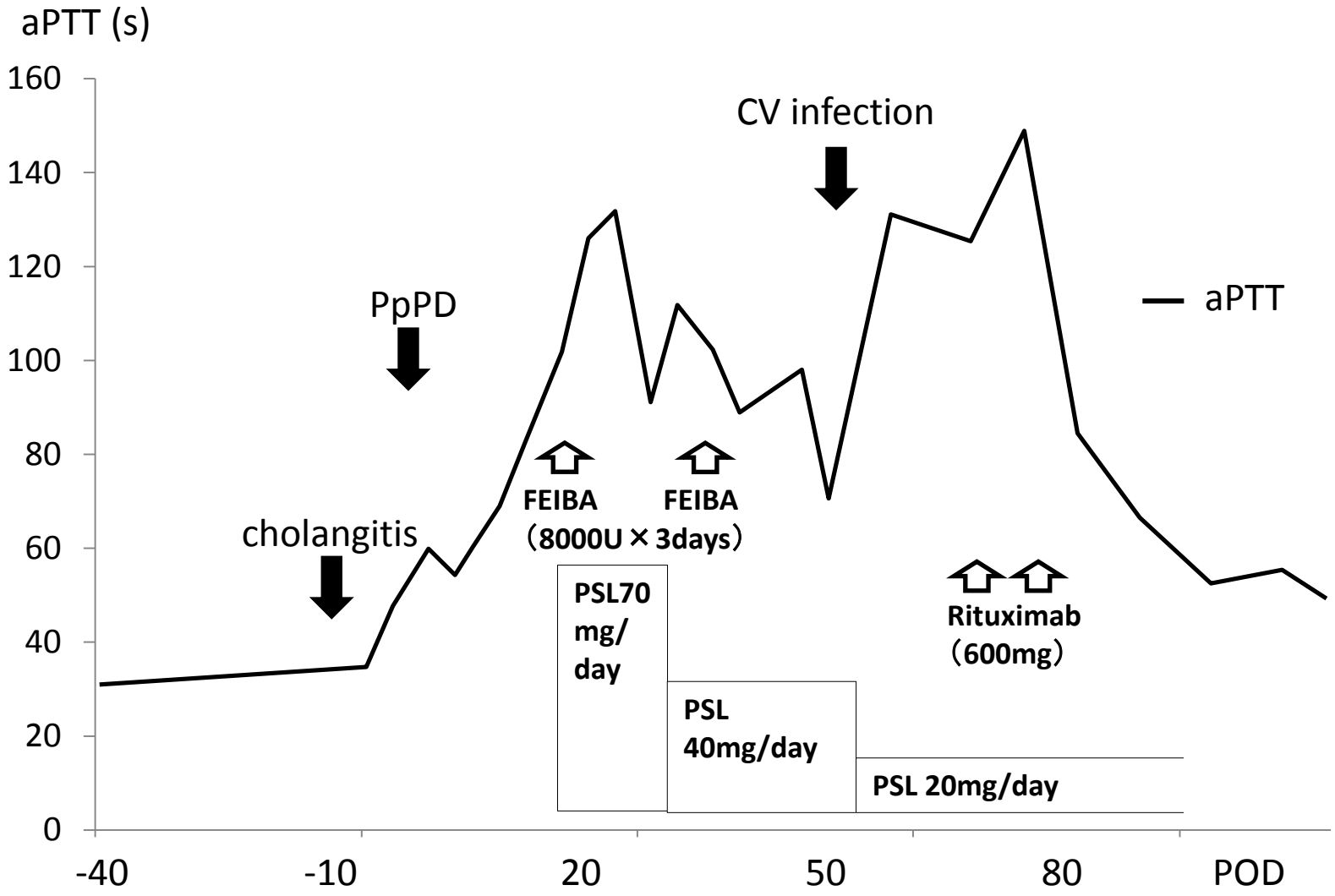
aPTT (s)
160
140
120
100
80
60
40
20
0
-40
-10
20
50
80
POD
CV infection
PpPD
cholangitis
FEIBA
FEIBA
（8000U × 3days）
PSL70 mg/ day
PSL 40mg/day
PSL 20mg/day
Rituximab
（600mg）
aPTT

Fig. 2

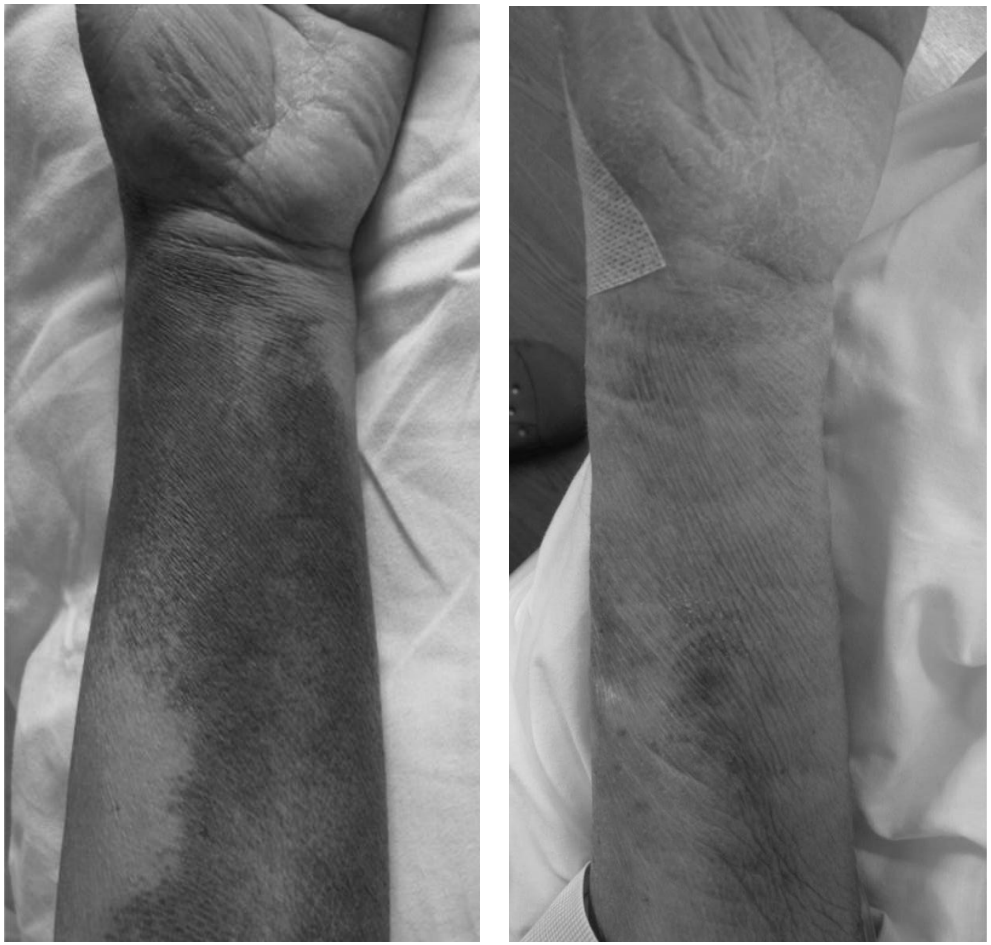

Fig. 3