CASE REPORTS

Thrombotic thrombocytopenic purpura associated with *Klebsiella* pneumonia in the background of alcoholic liver cirrhosis

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ABSTRACT

A 75-year-old male patient with alcoholic liver cirrhosis was emergently admitted due to systemic convulsion and *Klebsiella* pneumonia. He was referred to us due to severe thrombocytopenia (7,000/μl), and we suspected thrombotic thrombocytopenic purpura (TTP) considering the coexistence of hemolytic findings and neurological symptoms. We promptly performed plasma exchange and administration of corticosteroids, resulting in full recovery of symptoms and laboratory findings in a week. The diagnosis of TTP was confirmed by severely decreased ADAMTS13 activity (less than 0.5%) and detection of ADAMTS13 inhibitor. In this case, we speculated that TTP was triggered by *Klebsiella* pneumonia in the background of advanced alcoholic liver cirrhosis. This is the first report describing the complication of *Klebsiella* pneumonia and TTP. It is important to be aware that patients complicated with severe liver disease could be vulnerable to TTP.

Key Words: Thrombotic thrombocytopenic purpura, ADAMTS13, Alcoholic liver cirrhosis, *Klebsiella* pneumonia

1. INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and various organ dysfunctions. TTP is caused by dysfunction of a disintegrin-like metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13), a metalloprotease that cleaves von Willebrand factor (VWF). Lack of ADAMTS13 activity leads to excessive formation of very large multimers of VWF and subsequent microthrombi in small vessels, thus resulting in microcirculatory disturbances bringing about renal insufficiency and psychosomatic symptoms.[1,2]

TTP consists of an acquired disease, which occurs frequently in elderly men in Japan,[3] and a rare congenital disease known as Upshaw–Schulman syndrome.[4] Inactivation of ADAMTS13 in acquired TTP is caused by an autoantibody to ADAMTS13, known as ADAMTS13 inhibitor. It has recently been reported, however, that ADAMTS13 activity can decline in various conditions, such as liver cirrhosis and systemic inflammation.[5,6] In some cases, TTP could be caused by complicated mechanisms.

Here, we report a case of TTP that occurred in the background of alcoholic liver cirrhosis and was possibly triggered by *Klebsiella* pneumonia. This case highlights the complex pathophysiology of TTP in a patient with severe liver disease.

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Table 1. Laboratory findings at presentation

Complete Blood Test		
WBC	6,890	/μl
Neut	80.7	%
Lymp	11.2	%
Mono	7.8	%
Eosi	0.3	%
Hb	7.9	g/dl
Ht	22.2	%
MCV	91.4	fl
Ret	63	‰
PLT	7,000	/μl
Coagulation		
PT-INR	1.28	
APTT	35.1	sec
Fib	231	mg/dl
FDP	15.2	μg/ml
D-dimer	8.4	μg/ml
Urinalysis		
S.G.	1.025	
pH	6	
Protein	(±)	
Glucose	(4+)	
Urobilinogen	(2+)	
O.B.	(2+)	
Ketone	(–)	

Serum Biochemistry		
T-bil	3.49	mg/dl
D-bil	1.62	mg/dl
AST	44	IU/L
ALT	12	IU/L
ALP	839	IU/L
LDH	559	IU/L
γ-GTP	212	IU/L
ChE	65	IU/L
BUN	24.7	mg/dl
Cr	0.75	mg/dl
UA	3.3	mg/dl
Na	127	mEq/L
Cl	94	mEq/L
K	3.9	mEq/L
Ca	8.4	mg/dl
IP	2.1	mg/dl
NH_3	58	μg/dl
TP	7.2	g/dl
ALB	2.3	g/dl
CRP	5.14	mg/dl
Glu	639	mg/dl
HbA_{1c}	9.9	%

Immunology		
Haptoglobin	< 10	mg/dl
IgG	1,827	mg/dl
IgA	1,278	mg/dl
IgM	138	mg/dl
Direct Coombs test (1+; nonspecific)		
Indirect Coombs test (–)		
Antinuclear antibody (–)		
PR3-ANCA (–)		
MPO-ANCA (–)		
ADAMTS13 activity < 0.5%		
ADAMTS13 inhibitor 0.6 Bethesda units/ml		

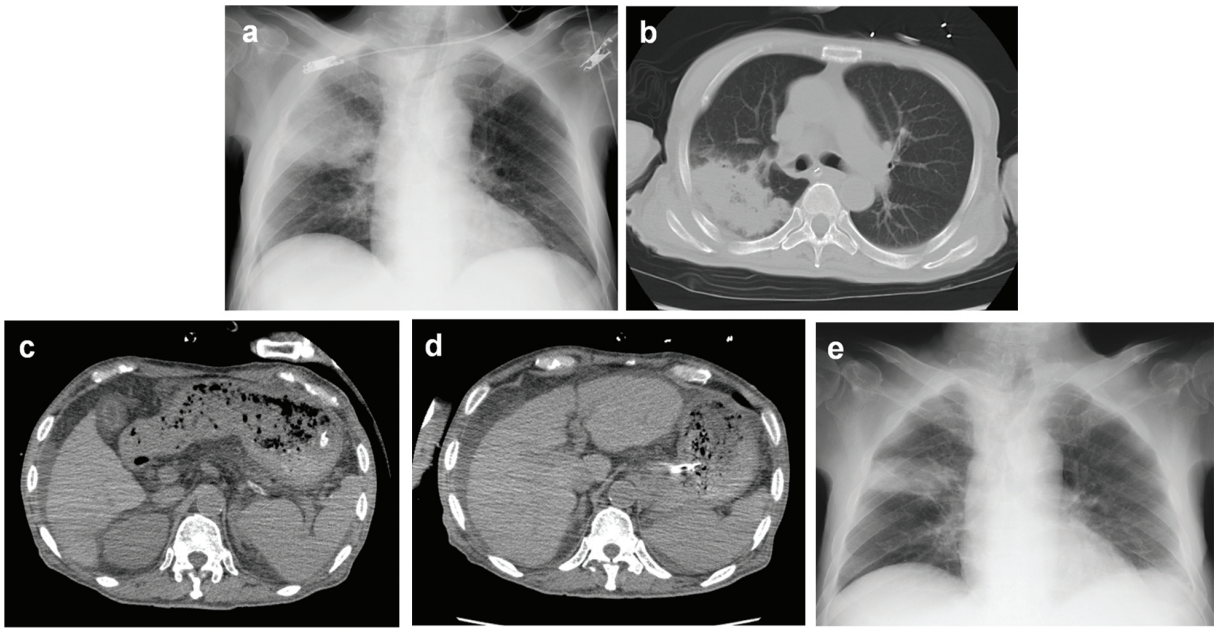

Figure 1. Radiological findings on admission. (a, b) Pneumonia in the right upper lobe was detected by X-ray and Computed tomography (CT); (c, d) CT of the abdomen showed atrophic liver and ascites, consistent with liver cirrhosis. Splenomegaly was not conspicuous; (e) A week after initiation of antibiotic therapy, pneumonia was well controlled

2. Case report

A 75-year-old male patient was admitted to the emergency department of our hospital due to systemic convulsion, which was well controlled by anticonvulsants, and prolonged disturbance of consciousness. He had previously been diagnosed with diabetes mellitus and severe alcoholic liver cirrhosis, which had not been controlled well because of alcohol abuse. On admission, he was mildly febrile (body temperature, 37.8°C) with stable vital signs and respiratory state. He was in a delirium state with disorientation; otherwise no apparent neurological deficits were detected on examination. Laboratory findings at presentation are shown in Table 1. Complete blood test revealed severe thrombocytopenia and moderate anemia with increased reticulocytes. White blood cell count was normal. Peripheral blood smear presented sporadic red cell fragmentation. Coagulatory function was mildly disturbed. Serum biochemistry indicated elevation of lactic dehydrogenase and indirect bilirubin. Transaminase level was slightly elevated. Cholinesterase and albumin were markedly reduced. There was no renal dysfunction. The C-reactive protein level was moderately elevated. Ammonia level was not elevated. There was marked hyperglycemia without ketonuria. X-ray and computed tomography (CT) revealed pulmonary consolidation in the upper right lung, suggesting acute pneumonia (see Figure 1a, b). CT also revealed atrophic changes of the liver with ascites suggesting severe liver cirrhosis (see Figure 1c, d), which was scored as C according to the Child–Pugh classification. His usual medications were branched chain amino acid, ursodeoxycholic acid (for liver cirrhosis), telmisartan, amlodipine (for hypertension), lansoprazole (for gastroesophageal reflux disease), zonisamide, levetriacetam (for seizure) and insulin; they had been prescribed for several months.

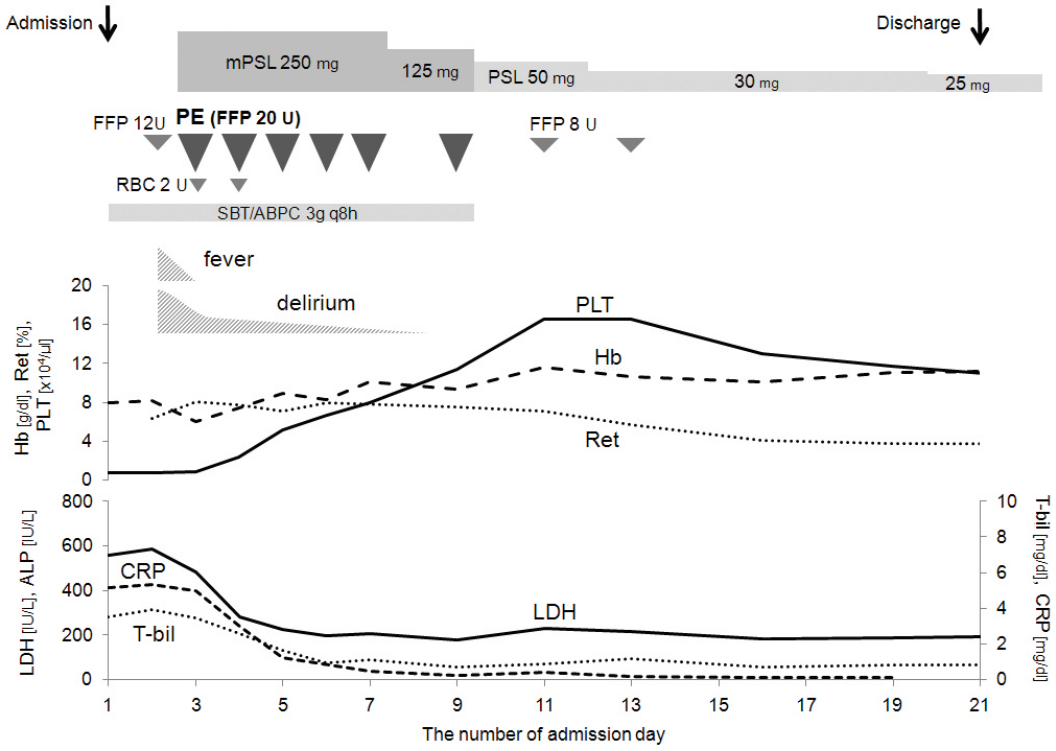

Figure 2. Clinical course after admission

ALP: alkaline phosphatase; CRP: C-reactive protein; FFP: fresh frozen plasma; Hb: hemoglobin; LDH: lactic dehydrogenase; mPSL: methylprednisolone; PE: plasma exchange; PLT: platelet; PSL: prednisolone; RBC: red blood cell; Ret: Reticulocyte; SBT/ABPC: sulbactam/ampicillin; T-bil: total bilirubin.

Due to severe thrombocytopenia, the patient was referred to us the day after admission, and we suspected TTP considering the findings of hemolytic anemia with schistocytes and marked thrombocytopenia. His clinical course is shown in Figure 2. We immediately administered fresh frozen plasma (FFP) and subsequently performed plasma exchange (PE) every day from the 3rd admission day. We also administered methylprednisolone (125 mg twice daily) to suppress possible ADAMTS13 inhibitor. His consciousness level was rapidly ameliorated. Findings of hemolysis also improved immediately, and platelet level increased gradually within a few days. On the 11th admission day, platelet count was

normalized, and PE was then stopped. Sputum culture at the time of admission yielded *Klebsiella* pneumoniae with favorable sensitivity for most antibiotics, and the pneumonia was well controlled by antibiotics (sulbactum/ampicillin, 3 g q8h) (see Figure 1e). ADAMTS13 activity was undetectable at the time of admission, and a diagnosis of TTP was established. ADAMTS13 inhibitor level was slightly elevated (0.6 Bethesda units/ml). None of his usual medications described above have been reported to be associated with TTP. After discontinuation of PE, steroid was tapered without recurrence of TTP. His general condition also recovered well, and he was discharged on the 21st admission day. ADAMTS13 activity recovered favorably, and thereafter steroid was further tapered without recurrence of disease. ADAMTS13 activity has been potentiated at a relatively low level for 3 months. After remission, ADAMTS13 inhibitor was transiently detected (0.6 Bethesda units/ml), but disappeared thereafter (see Figure 3). VWF multimer analysis of plasma (see Figure 4) revealed existence of substantial amount of unusually large VWF multimers (UL-VWFM) in remission phase as well as in acute phase of TTP. The total amount of VWF antigen was also increased in remission state of TTP, which is considered to be caused by alcoholic liver cirrhosis.

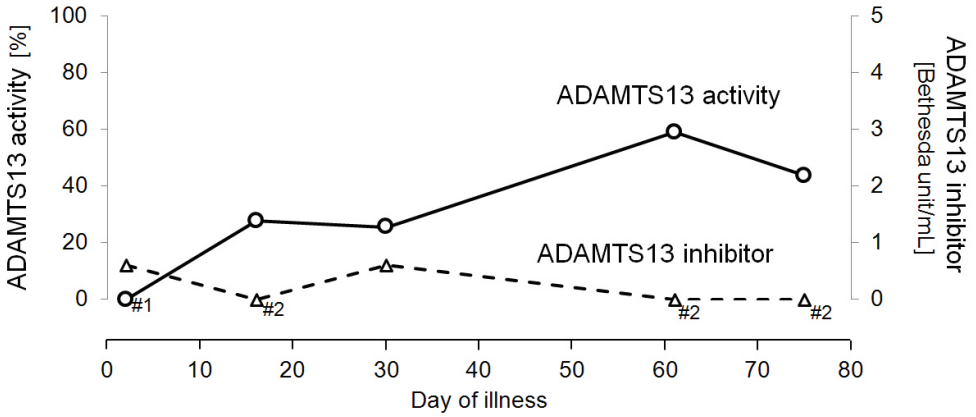

Figure 3. Changes in ADAMTS13 activity and inhibitor titer
#1 ADAMTS13 activity was below 0.5%; #2 ADAMTS13 inhibitor titer was below 0.5 Bethesda units/ml.

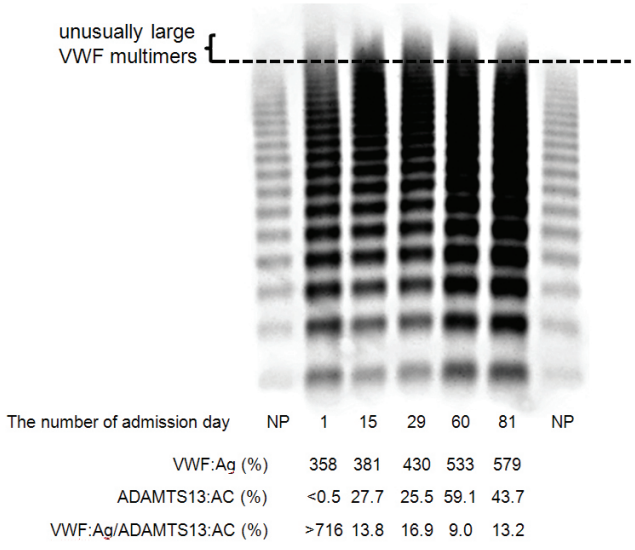

Figure 4. VWF multimer analysis
AC: activity; Ag: antigen; NP: normal plasma.

3. Discussion

TTP is caused by inhibition of metalloprotease ADAMTS13 activity by autoantibody (called ADAMTS13 inhibitor), resulting in accumulation of ultra-large VWF multimers and platelet thrombi formation in the systemic microcirculation.[7] It was reported that the inhibitor titer is varied in each case, and it remains controversial whether the inhibitor level can be used to predict treatment efficacy or clinical prognosis.[8,9] However, Kremer Hovinga *et al.* recently reported that a low inhibitor titer of (less than 2 BU/ml) was associated with higher survival rate among patients with low ADAMTS13 activity (< 10%), in a population-based study of TTP.[10] Consistent with this report, in the present case, ADAMTS13 activity at diagnosis was extremely low (< 0.5%) with low inhibitor level (0.6 Bethesda units/ml), and short-term and relatively few plasma exchanges were sufficient for remission of TTP.

Decreased ADAMTS13 activity has also been documented in various conditions, such as liver disease and systemic inflammation. Uemura *et al.* analyzed ADAMTS13 activity and its related parameters in plasma from 33 patients

with chronic hepatitis and 109 patients with liver cirrhosis (LC), and reported that ADAMTS13 activity decreased with increasing severity of liver disease.[5] They also showed severe deficiency (< 3% of controls) in five cases of end-stage LC, one of whom experienced clinical TTP, and detection of plasma ADAMTS13 inhibitor in 83% of patients with severe to moderate ADAMTS13 activity deficiency. As ADAMTS13 is produced by hepatic stellate cells,[11] it is reasonable that ADAMTS13 activity is diminished in proportion to the degree of liver damage resulting in a decrease of hepatic stellate cells. Moreover, Ishikawa *et al*. reported decreased ADAMTS13 activity and increased VWF in patients with alcoholic hepatitis, which could be induced not only by proinflammatory cytokinemia but also by ADAMTS13 inhibitor.[12] Furthermore, Reuken *et al*. recently reported that systemic inflammation complicating advanced cirrhosis is accompanied by reduced activity of ADAMTS13, promoting a prothrombotic function of VWF.[6] In this case, it was assumed that TTP was triggered by the inflammatory state due to *Klebsiella* pneumonia in the background of advanced alcoholic liver cirrhosis. It is somewhat questionable, however, whether ADAMTS13 activity was substantially elevated after remission of TTP; this might be explained by improvement of his lifestyle and total abstinence from alcohol.

To our knowledge, this is the first case report of TTP associated with *Klebsiella* pneumonia. With regard to the relationships among TTP, ADAMTS13, and infectious diseases, it has been reported that ADAMTS13 activity is decreased in sepsis patients.[13–15] This could be at least partially explained by significant inhibition of ADAMTS13 activity by the inflammatory cytokine interleukin-6, resulting in a diminished rate of cleavage of ultra-large VWF multimers.[16] Peigne *et al*. recently reported that septic shock could be associated with partial functional deficiency of ADAMTS13, the mechanism of which may be related to IL-6-mediated inhibition, based on a prospective cohort study of 72 patients with septic shock.[17] They also reported that ADAMTS13 functional deficiency can be a prognostic factor for mortality in septic shock patients. Other than sepsis, cases of TTP associated with infection have been reported sporadically with various pathogens, such as influenza virus,[18–20] Brucella,[21] Mycoplasma,[22,23] *etc*. In these cases, TTP could be caused by ADAMTS13 inhibitor production triggered by infection, as well as decreased ADAMTS13 activity by inflammatory cytokines, including interleukin-6.

In addition, it was revealed that UL-VWFM existed even in a remission state of TTP in the present case. This suggests that the patient has a thrombotic tendency in a natural state, which is probably influenced by alcoholic liver cirrhosis. Therefore, it is possible that this patient is potentially at risk of outbreak of TTP, and special caution should be paid to the recurrence of TTP.

In summary, we reported a case of TTP that was possibly triggered by *Klebsiella* pneumonia in the background of advanced alcoholic liver cirrhosis. It is important to be aware that patients complicated with severe liver disease could be vulnerable to TTP, as prompt and appropriate diagnosis of TTP could be difficult due to the complex clinical conditions in such patients and delay of treatment initiation could be fatal.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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