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Case Report

Deep vein thrombosis and pulmonary thromboembolism in a patient with eosinophilia and obesity

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A 46-year-old female patient with deep vein thrombosis (DVT) and pulmonary embolism complicated with disseminated intravascular coagulation was admitted to our hospital. She was treated with urokinase and repeated plasma exchange and with the administration of low-molecular-weight heparin coupled with a high dose of glucocorticoid after inferior vena cava (IVC) filter placement. As the etiology of DVT, blood tests showed no evidence of antiphospholipid syndrome or protein S/C deficiency except for hypereosinophilia and obesity with a high body mass index (34 kg/m^2). Activated protein C (APC) resistance was not detected. Eosinophilia coupled with remarkable obesity was considered to be the trigger of DVT in this patient. After intensive therapy along with strict anti-coagulant agents, effective reduction of thrombosis in both the IVC and pulmonary arteries was observed along with improvement of the coagulation system.

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Introduction

Deep vein thrombosis (DVT) is a fatal disorder because it secondarily causes pulmonary thrombosis (1). Various conditions, including obesity, the use of oral contraceptives, malignancy, antiphospholipid syndrome (APS) and some genetic defects (2-4) are known to be etiologically related to DVT. Furthermore, Sherer et al. (5) reported that thromboembolism was observed in a patient with transient eosinophilia. Obesity was also reported to be related to DVT from studies using animal models (6). It has also been shown that obesity is one of the endogenous risk factors for DVT (7). In this report, we demonstrate the successful treatment of DVT with disseminated intravascular coagulation (DIC) and discuss the etiology of DVT.

Case report

On August 2, 2005, a 46-year-old female who had suffered from bronchial asthma and obesity entered our hospital with symptoms of edema and petechia in the lower extremities (Figure 1). She had a family history of autoimmune disorders, as her mother suffered from rheumatoid arthritis and her younger sister had systemic lupus erythematosus (SLE) with secondary Sjögren's syndrome. Her height was 154 cm and her body weight was 76.5 kg, indicating that her body mass index (BMI) was 34 kg/m^2. There was no obvious anemia, jaundice or superficial lymph nodes swelling. Both heart and breath sounds were normal, although there was edema of both lower extremities with petechia.

Laboratory findings on admission (Table 1) showed severe thrombocytopenia to 2.5x10^4/mm^3 and elevation of eosinophils to

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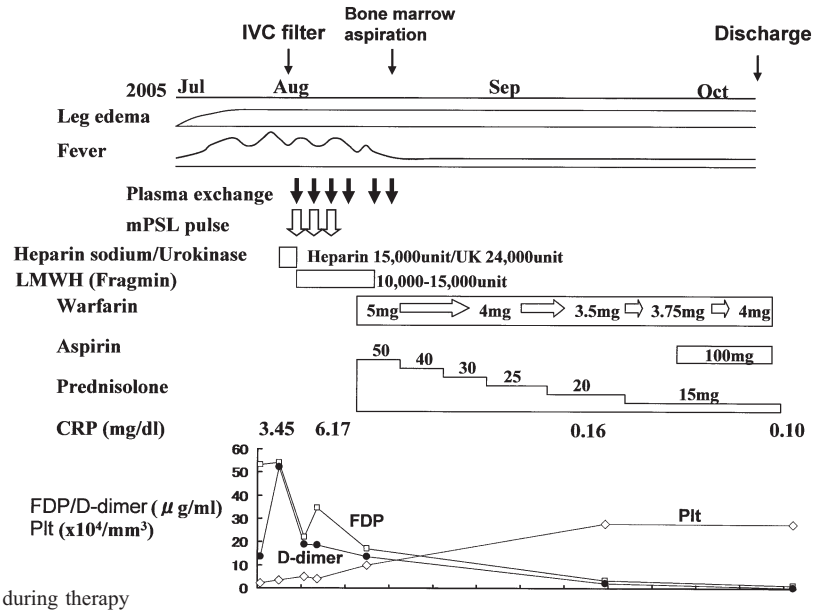

Figure 1. Clinical course during therapy
The patient was admitted to our hospital with leg edema, petechia of her legs and severe thrombocytopenia on August 2nd. Because deep vein thrombosis and pulmonary embolism were found by imaging studies such as magnetic resonance angiography and contrast computed tomography, both heparin sodium and urokinase (UK) were administered followed by inferior vena cava (IVC) filter placement. Based on the diagnosis of disseminated intravascular coagulation based on petechia, severe thrombocytopenia, and remarkable elevation of both fibrinogen degenerating product (FDP) and D-dimer, repeated plasmapheresis and methylprednisolone (mPSL) pulse therapy were adopted, resulting in improvement of the clinical symptoms and laboratory data including platelets, C-reactive protein, FDP and D-dimer. Following the administration of low-molecular-weight heparin (LMWH), warfarin and oral prednisolone were started, and the prednisolone was tapered along with the aspirin. Finally, the patient was discharged on October 13, and was prescribed 4mg of warfarin, 15 mg of oral prednisolone and 100 mg of aspirin.

2,162/ mm^3, and serum fibrin degradation products (FDP) and D-dimer with slight reduction of prothrombin time. In blood chemistry, lactate dehydrogenase and C-reactive protein were elevated to 366 IU/l and 3.45 mg/ml, respectively. With regard to coagulation factors, factor VIII was over 200%, but factors IX and XI were almost within normal range. The laboratory findings along with the clinical manifestations fulfilled the criteria of DIC defined by the Japanese Health and Welfare Ministry because petechia, thrombocytopenia and the elevation of serum FDP amounted to 7 points in the scoring of DIC. Serum IgG, rheumatoid factor, serum complement, anti-double-strand DNA antibody, anti-Sm antibody, anti-ribonucleoprotein antibody, anti-SS-A antibody and immune complex C1q were all negative. Total homocysteine was within the normal limits (12.3; normal range: 3.0-14 nmol/ml). Regarding thrombocytopenia, lupus anticoagulant and anti-CLbeta2GPI were negative, although the platelet-associated IgG (PA-IgG) level was elevated to 156.8 ng/ml (normal range; 9.0-25.0 ng/ml). A bone marrow smear demonstrated hyperplasia with increased megakaryocytes, but there was no obvious infiltration of abnormal cells. To exclude thrombotic thrombocytopenic purpura (TTP), we measured the ADAMTS13 activity (8), which revealed a cleaving enzyme for von Willebrand factor (vWF) and showed a slight reduction (16 %) of the activity, although such a reduction was not specific for typical TTP. Neither fragmented erythrocytes nor mental disturbance was observed. IgM antibodies to the EB virus and Parvo B19 virus were negative, although IgG antibodies for these viruses were positive. Repeated cultures of various specimens and a test for ß-D glucan and

Table 1. Clinicopathological profiles of patients and summary of results

Variables	On admission	On discharge	Normal range	unit
White blood cell	8,700	6,700	3,500-9,000	/mm^3
Eosinophil	26	0	0-5	%
Red blood cell	424x10^4	452x10^4	380-480 x10^4	/mm^3
Hemoglobin	8.9	12.8	13.0-17.0	g/dl
Hematocrit	29.5	41.0	34.0-45.0	%
Platelet	2.5x10^4	27.4 x10^4	14-33 x10^4	/mm^3
PT	76 (1.13)	32 (2.23)	82-127	% (INR)
APTT	34.0	NT	30-40	sec
Fibrinogen	164	NT	200-400	mg/dl
AT-III	106	126	80-128	%
Serum FDP	53.3	1.3	<5	μg/ml
D-dimer	13.6	0.3	<1	μg/ml
Protein S	80	NT	60-150	%
Protein C	81	NT	70-150	%
Factor VIII	>200	NT	62-145	%
Factor IX	70	NT	74-149	%
Factor XI	117	NT	73-136	%
Creatinine	0.8	0.7	0.4-1.1	mg/dl
AST	33	10	13-33	IU/l
ALT	37	18	8-42	IU/l
LDH	366	NT	119-229	IU/l
γ-GTP	107	34	10-47	IU/l
CRP	3.45	0.15	<0.17	mg/dl

NT; not tested, PT prolonged to 32 % on discharge because treatment with warfarin was started. Factors VIII, IX and XI were not examined after plasma exchange (PE) because fresh frozen plasma was administered by PE. INR; international normalized ratio. AST: aspartate transaminase, ALT: alanine transaminase, FDP: fibrin degradation products, LDH: lactate dehydrogenase, PT: prothrombin time, APTT: activated partial thromboplastin time

cytomegalovirus antigen showed no obvious pathogens such as bacteria, fungi, cytomegalovirus or tuberculosis. No vegetation was found by transthoratic echocardiogram.

According to the magnetic resonance (MR) angiography findings which showed obstruction of the left common iliac vein and femoral vein on August 2, anti-coagulation therapy including 240,000 units of urokinase and 15,000 units of heparin sodium per day was initiated. However, chest CT was performed on August 2 because the patient experienced hemosputum, showing a subpleural trapezoidal shadow. Because DVT along with pulmonary embolism were suspected, a permanent filter (TRAPEASE® Permanent Vena Cava Filter, Johnson & Johnson, CA, U.S.A.) was urgently installed into the IVC on the same day to prevent additional pulmonary embolism. However, contrast CT findings on August 7 demonstrated a venous thrombus in the inferior vena cava (IVC) (Figure 2A) and bilateral femoral veins (Figure 2B) with apparent pulmonary thromboembolism (Figure 2C). Repeated plasma exchange and an intravenous administration of a high dose of glucocorticoid were then performed after a filter was placed in the IVC (Figure 1). We selected both plasma exchange and the administration of high dose glucocorticoid for the possible existence of underlying autoimmune diseases.

For the purpose of determining the etiology of this refractory venous thrombus, we tried to find activated protein C (APC) resistance (COATEST® APC™ Resistance; CHROMOGENIX, Lexington, MA, U.S.A.), because the presence of APC resistance would imply the presence of a mutation of factor V Leiden. However, the APC ratio of this patient was 2.4, which was the same as that of the normal control. The APC ratio of the positive control was 1.6, which was obviously lower than that of the normal control and this patient. Informed consent for measurement of APC resistance or genetic

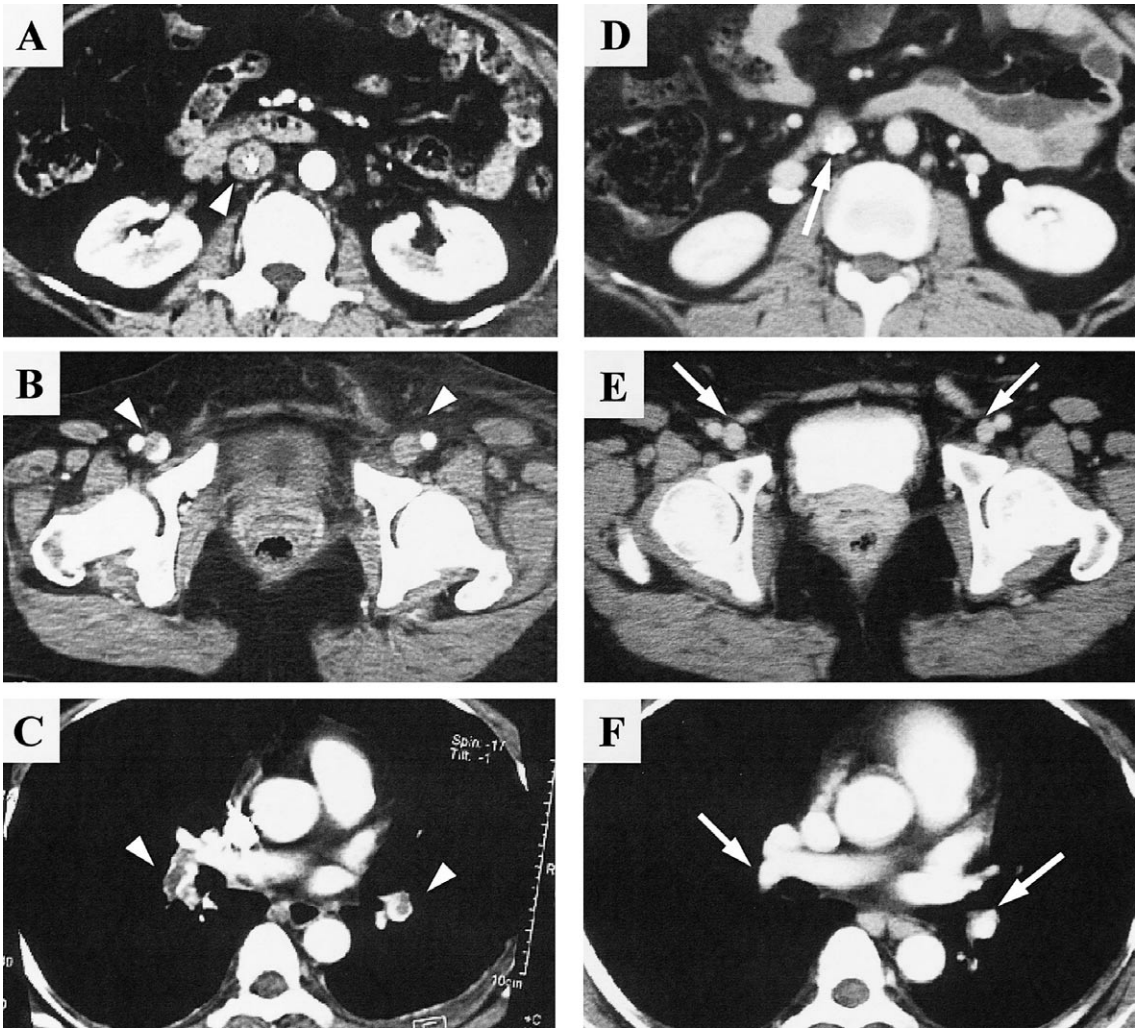

Figure 2. Improvement of both deep vein thrombosis and pulmonary embolism after intensive therapy
A. Just after the initiation of treatment, the inferior vena cava (IVC) was totally obstructed at the portion of the IVC filter (arrow head). **B.** The left and right femoral veins were completely and partially obstructed at the beginning of the treatment, respectively (arrow heads). **C.** Pulmonary arteries (arrow heads) were also obstructed as captured by contrast computed tomography at the beginning of the intensive therapy. **D.** After intensive therapy followed by strict anti-coagulation management, the obstructed IVC was reopened (arrow). **E.** The left and right femoral veins were patent after intensive therapy (arrows). **F.** After the therapy, the low-density area in the pulmonary arteries was obviously reduced (arrows).

defects was obtained according to the guidelines of the ethical committee of our institution.

After intensive therapy including repeated plasma exchange (6 times) and the intravenous administration of a high dose of glucocorticoid, the patient was treated with 50mg of oral prednisolone and 5mg of warfarin along with 100mg of aspirin, resulting in an improvement of DIC. Finally, the patient was discharged on October 13 2005 and was prescribed 15mg of oral prednisolone, 4mg of warfarin with an INR around 2.2 and 100mg of aspirin. Follow-up CT revealed improvement of the thrombosis of the IVC and pulmonary arteries (Figs. 2D, 2E and 2F). Upon discharge, eosinophilia was also normalized, as shown in Table 1. Strict anti-coagulant management after discharge was necessary because a worsening tendency of the leg edema was observed when the effect of warfarin was attenuated, although the follow-up CT findings showed no newly-developed thrombosis.

Discussion

Some reports have indicated that the percentage of eosinophils in leucocytes reached 43.5-60 % when pulmonary embolism or systemic thrombophlebitis existed (9, 10). Regarding the pro-coagulant effect of eosinophilia, Mukai et al. (11) previously reported that major basic protein, which was one of the eosinophil-derived cationic granule proteins, could activate the anticoagulant protein C by means of thrombin. Furthermore, obesity itself might have the potential to induce DVT in accordance with eosinophilia synergistically. Regarding obesity as one of the risk factors of DVT, Abdollahi et al. (12) reported that individuals who have a BMI higher than 30 kg/m^2 showed twice the risk for DVT as age and sex-matched controls. They also revealed that obese individuals had increased levels of factors VIII and IX, which was consisted with our case. Because our case showed the presence of both obesity and eosinophilia, such a synergistically increased risk of thrombosis may have been present. With regard to the relationship between obesity and the risk of thrombosis, a previous report (6) demonstrated that leptin-dependent platelet aggregation and subsequent arterial thrombosis occurred in obese (*ob*/*ob*) mice. Because leptin did not induce the aggregation of platelets from leptin receptor-deficient mice, the receptor-dependent effect of leptin is considered in obesity. These new insights should be considered as one of the risks of thrombosis in cases of severe DVT patients with obesity.

Although we failed to detect APC resistance, which suggests the existence of factor V mutation, eosinophilia per se was reported to be a risk factor for DVT (2) because the acceleration of thrombosis in the presence of eosinophilia was related to the impairment of thrombomodulin function. We should take notice in both cases with and cases without mutations when we investigate DVT patients with eosinophilia.

We urgently installed a permanent IVC filter because pulmonary thromboembolism had occurred despite initial anti-coagulation therapy with urokinase and heparin sodium. We selected a permanent IVC filter because MR angiography revealed the existence of DVT in the left common iliac vein and femoral vein, and we could not exclude underlying autoimmune disorders that had the potential to induce chronic or recurrent pulmonary thromboembolism. Regarding intensive therapy followed by the anti-coagulation prophylaxis, we initially employed repeated methyl prednisolone pulse therapy and plasma exchange along with heparin or low-molecular-weight heparin because of the existence of immunological disorders. Although obvious underlying autoimmune disorders were not detected in this case, the family history along with the presence of PA-IgG suggested that the existence of autoimmune diseases might be associated with the occurrence of DVT. Therefore, we carefully followed up the clinical symptoms and laboratory findings related to the autoimmune disorders.

In summary, we experienced DVT complicated with obesity and eosinophilia and successfully treated it with intensive therapy followed by strict anti-coagulant management. When patients demonstrate DVT, both obesity and eosinophilia should be considered possible risk factors.

Abbreviations: APC: activated protein C, APS: antiphospholipid syndrome, BMI: body mass index, DIC: disseminated intravascular coagulation, FDP: fibrin degradation products, PA-IgG: platelet-associated IgG, ITP; idiopathic thrombocytopenic purpura, IVC: inferior vena cava, MR: magnetic resonance, MTHFR: methylenetetrahydrofolate, SLE: systemic lupus erythematosus, TTP; thrombotic thrombocytopenic purpura, vWF; von Willebrand factor

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