CASE REPORT
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Hereditary protein S deficiency presenting acute pulmonary embolism

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Protein S deficiency is one of the several risk factors for thrombophilia and can cause blood clotting disorders such as deep vein thrombosis and pulmonary embolism. A 54-year-old man was admitted with the complaint of dyspnea and was diagnosed with pulmonary embolism. The patient had very low level of free protein S, total protein S antigen, and protein S activity (type I protein S deficiency). In history taking, we found that his mother, 78 year old, had a history of same disease 10 years ago, and confirmed the pronounced low level of protein S. The patient's son also had very low level of protein S, however there had not been any history of pulmonary embolism yet. This case study suggests that asymptomatic persons with a family history of protein S deficiency and pulmonary embolism should be checked regularly for early detection of the disease, as protein S deficiency can be suspected.

Keywords: Pulmonary embolism; Protein S deficiency; Family history

INTRODUCTION

Protein S deficiency is a blood clotting disorder that affects just a few thousand people worldwide. Decreased total or free protein S antigen levels and impaired function lead to decrease degradation of factor Va and factor VIIIa and increase the risk of thrombosis such as deep vein thrombosis and pulmonary embolism. Protein S deficiency is uncommon in the general population (0.2% to 0.5%), and is only detected in 1% to 3% of patients with venous thromboembolism [1]. Association of familial protein S deficiency with recurrent thrombosis was first reported in 1984 [2], however there have been very few reports in Korea. Here, we report a case of a family history of pulmonary embolism with protein S deficiency over 2 generations and protein S deficiency without the onset of the disease in the third generation.

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CASE

A 54-year-old man was admitted in the hospital with dyspnea (NYHA functional class III) and left foot edema for 3 months. He had a history of hypertension and diabetes since 5 years ago. Medications related with coagulation system were not administered at the time of initial presentation. He was 30 pack-year ex-smoker and stopped smoking 1 year ago. The patient had no history of cardiovascular heart disease, hematologic disease or connective tissue disease. On admission, the blood pressure was 138/88 mm Hg with a pulse rate of 128 beats/min, and the physical examination demonstrated left pretibial pitting edema with erythematous rash. Computed tomography (CT) scan showed large burden of bilateral pulmonary thromboembolism and extensive deep vein thrombus in left lower extremity and infrarenal inferior vena cava to the right common iliac vein (Fig. 1). D-dimer level was highly elevated (>20 ug/mL). Other laboratory findings for suggesting disseminated intravascular coagulation as follows, platelet 163,000/mm^3 (140,000-400,000), prothrombin time 93% (80-120), activated partial thromboplastin time 39.9 sec (29-45), fibrinogen 323 mg/dL (170-350). The patient was diagnosed with pulmonary embolism and intravenous

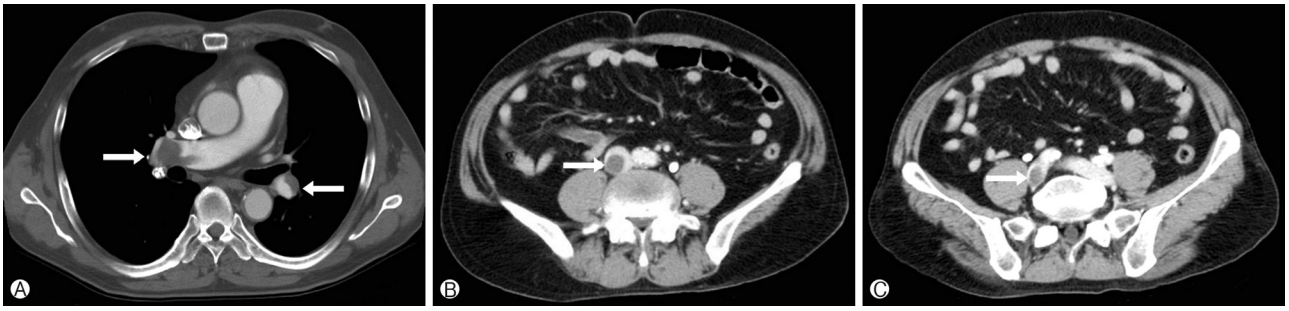

Fig. 1. Axial images of chest and abdominal contrast-enhanced computed tomography (CT) scan. At the time of diagnosis, chest CT scan showed large burden of bilateral pulmonary thromboembolism (A) and abdominal CT scan showed extensive deep vein thrombus in infrarenal inferior vena cava (B) to the right common iliac vein (C).

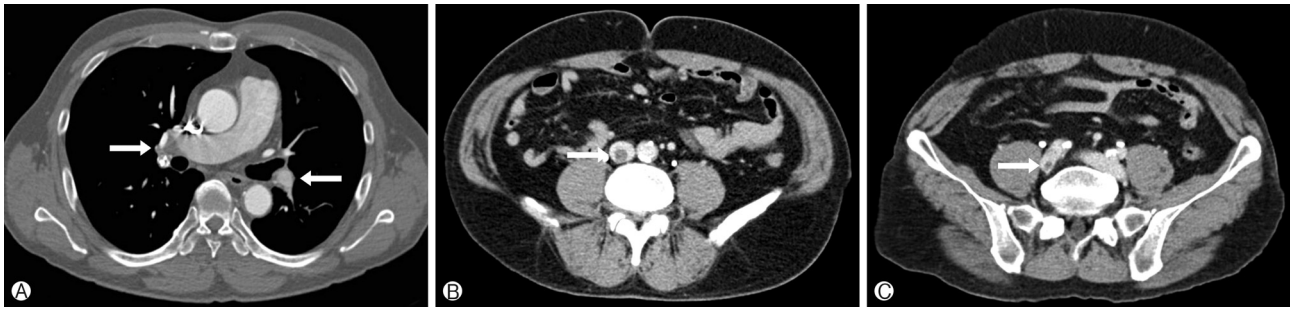

Fig. 2. After 3 months of anti-coagulation treatment, follow-up computed tomography scans showed the decrease size of thrombus both in pulmonary artery (A) and infrarenal inferior vena cava (B) to the right common iliac vein (C) (Fig. 2).

heparinization was started and switched to oral warfarin with the 5 days overlapping period. Before the anticoagulation therapy, we examined the various kinds of hematologic tests involving the coagulation system. It showed normal levels of lupus anticoagulant and factor V (functional) and protein C activity, but free and total protein S antigen and protein S activity were very low at 17% (normal range 50% to 150%), 30% (normal range 60% to 150%), and 26% (normal range 73.7% to 146.3%), respectively. His antithrombin was slightly low at 78% (normal range 80% to 120%). After 3 months of anti-coagulation treatment, follow-up CT scans showed the decrease size of thrombus both in pulmonary artery (Fig. 2A) and infrarenal inferior vena cava (Fig. 2B) to the right common iliac vein (Fig. 2C).

From family history taking, we found the patient's mother also was diagnosed with pulmonary thromboembolism 10 years ago and was followed without medication. But, 4 months ago, she was admitted in the hospital with general weakness and left lower extremity edema. CT scan showed extensive deep vein thrombus in left lower extremity. She is currently taking warfarin. With the suspicion of hereditary coagulation disorder, we checked the hematologic test of coagulation system in the patient's mother and his offspring (Fig. 3). In the case of patient's mother, there were not any abnormalities in anti-thrombin III, protein C, and lupus anticoagulant. Factor V Leiden mutation were not detected. However, the level of free and total protein S antigen were significantly

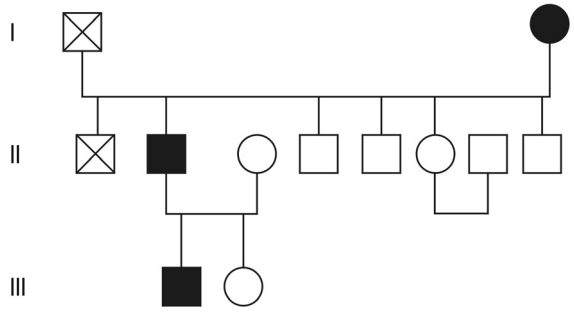

Fig. 3. Genealogy of pulmonary embolism and protein S deficiency. I-1, death; I-2, currently 78 years old, embolism onset at 67 years old. II-2, patient, 54 years old; His elder brother (II-1) experienced acute myocardial infarction and he died in his twenties. III-1, 24 years old; III-2, 20 years old; I-2, II-2 had histories of pulmonary embolism, I-2, II-2, III-1 had type 1 deficiency, and III-2 resembled type 2 deficiency.

Table 1. The level of protein S by each generation

Factor (%)	First generation mother	Second generation patient	Third generation	
			son	daughter
Free protein S antigen (normal range 50-100)	21	13	16	84
Total protein S antigen (normal range 60-150)	43	30	33	59
Functional protein S activity (normal range 73.7-146.3)	9	17	23	58

low at 21% and 43%, respectively. Her protein S activity also decreased to 9%. In the patient's son (24 years old), he also had very low level of free and total protein S and low protein S activity. However, there had not been any history of pulmonary embolism yet. On the other hand, the patient's daughter (20 years old) had a normal level of free protein S, and slightly decreased total protein S and protein S activity (Table 1).

After the anti-coagulation, the patient recovered from dyspnea and repeated CT scan showed resolution of thromboembolism of pulmonary artery. He discharged with the medication of warfarin and has been followed up without any events up to 6 months.

DISCUSSION

In this case, we found family history of pulmonary embolism and confirmed the protein S deficiency over three generations including the patient, his mother, and son. Protein S, a vitamin K-dependent plasma anticoagulant protein, functions as an enhancing cofactor to activated protein C (APC) in the inactivation of activated factors V (FVa) and VIII (FVIIIa) [3,4]. Protein S deficiency can be either hereditary or acquired from hepatic diseases or vitamin K deficiency. A study in 3,788 healthy Scottish blood donors showed a prevalence of hereditary protein S deficiency ranging from 0.03% to 0.13% [5]. In familial venous thrombosis, protein S deficiency was more common (2% to 10%) compare to healthy blood donor. Individuals with heterozygous protein S deficiency most commonly present with deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis, and increased risk of thrombosis five to ten-fold. Homozygous or compound heterozygous protein S deficiency is extremely rare and it is incompatible with life due to the extensive microvascular thrombosis. Acquired protein S deficiency has been found to be associated with oral contraception, liver disease, nephrotic syndrome, disseminated intravascular coagulation, and autoimmune disease or HIV infection. The risk of thrombosis in protein S deficiency is much higher if combined with genetic or acquired conditions predisposing for thrombosis [4,6].

The International Society for Thrombosis and Haemostasis Standardization Subcommittee has defined 3 types of hereditary protein S deficiency based on the plasma concentration of free, total protein S, and APC-cofactor activity. Type I deficiency is identified by low levels of free and total protein S with decreased APC-cofactor activity. Type II protein S deficiency is characterized by normal levels of total and free protein S antigen with low levels of APC-cofactor activity. Type III deficiency is characterized by normal levels of total antigen, low free protein S with decreased APC-cofactor activity [4,6,7]. According to previous studies, 95% of patients had quantitative (type I or type III), and 5% had qualitative (type II) deficiency [6]. Type II deficiency is very rare.

Hereditary protein S deficiency is an autosomal dominant disorder with variable clinical expression, and predisposes to venous thromboembolism. While protein S deficiency type I is a monogenetic disease due to PROS1 allelic heterozygosity, type III is most likely a more complex or heterogeneous disorder [8]. Previous studies indicate that low free protein S levels increased the risk of first venous thrombosis in relatively young people (mean age 39 years), which emphasizes that thrombophilic defects are risk factors for venous thrombosis at young age [9]. In this case, the patient's son had no history of venous thrombosis; however, since his free protein S and total protein S levels are declined, we assume that there is a high risk of him developing venous thrombosis in his 30's and regular examinations and checks were recommended until his 40's at least, in order to detect any signs of thrombosis early.

In Korea, there were several reports of pulmonary thromboembolism associated with protein S deficiency in the patients after coronary angiography [10], difficult-to-control asthma

[11], apical hypertrophic cardiomyopathy [12], and recurrent acute pulmonary embolism [13]. However these reports did not explore the family history or hereditary factor. In this case, protein S deficiency was observed through 3 generations, which may suggest a possible hereditary influence. However, there were some limitations to show definite hereditary relationship because we did not test the genetic abnormalities such as PROS1. Moreover, although pulmonary embolism was confirmed in the patient's mother, the results of radiographic and hemato-chemistry findings were not available. Finally, since the patient's mother was examined while the warfarin being administered, this might have affected her results of the Protein S level.

Regardless of the limitations, this case report suggests that the suspicion of protein S deficiency is required especially in the patient of venous thromboembolism without the typical risk factors. Especially, the hereditary protein S deficiency should be considered as one of the differential diagnosis in familial events of venous thromboembolism.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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