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Massive Pulmonary Thromboembolism Due To Activated Protein C Resistance and Protein S Deficiency

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Abstract

A 38-year-old woman, who presented with pulmonary embolism associated with thrombi in the main pulmonary arteries and enlarged right–sided chambers, was discovered to have both activated protein C resistance (APCR) and protein S deficiency. She had a heterozygous mutation for factor V Leiden. Especially in young individuals under 45 years of age and in the absence of risk factors, inherited prothrombotic defects should be considered. Hereditary APCR accounts for more thrombotic events than the other inherited deficiencies such as protein C and S and anti-thrombin. The presence of these factors together increases the risk and severity of thrombotic events.

Keywords: pulmonary thromboembolism, hereditary risk factors, APC resistance, protein S deficiency

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INTRODUCTION

APCR is the most common hereditary factor identified in young adults with thrombotic events, ranging from 20% to 50% [1]. A single missense mutation causing G/A transition in exon 10 of the factor V (FV) gene is correlated with APCR [2,3]. Most episodes occurring in patients with APCR are minor, but massive thromboembolism can occur in patients having homozygous mutation for FV Leiden or in the presence of multiple prothrombotic defects [1,4-6].

CASE PRESENTATION

A 38-year-old female admitted to our hospital with sudden onset of dyspnea and dizziness. A month before she had a chest pain which increased with deep breathing on the right side, but she did not admit to any doctor and healed spontaneously. She denied smoking, illicit drug use or alcohol use. There was no history of operation, trauma or immobilization. She did not take any medication, including oral contraceptives. There was past history of spontaneous abortus but her age at time of pregnancy was unknown. Her family history for thrombotic event was negative. Her mother had coronary arterial disease.

Physical examination revealed pulse rate of 118 per minute, blood pressure 90/50 mmHg, respiratory rate 48 per minute and body temperature of 36.8°C. Cyanosis was present and she had a loud P_2 sound and inspiratory crackles were heard in the right basal area on auscultation.

The laboratory findings on admission were: hemoglobin (Hb): 14.7 g/dl, hematocrit (Htc): 43.3%, WBC: 17500/mm^3, platelet (PLT): 170000/mm^3, lactate dehydrogenase (LDH): 643 U/L. Blood gase analysis showed that pH: 7.55, pCO_2: 22 mmHg, pO_2: 77 mmHg, and Sa O_2: 86%. Her chest radiograph showed cardiac enlargement (Figure 1).

Since the clinical signs and symptoms were suggestive of pulmonary embolism, 5000 IU heparin was given as intravenous bolus and followed by a continuous rate of 1000 IU/hr.

Technetium 99m perfusion scan of the lung revealed multiple subsegmental defects on the right lung and diffuse decrement on the left (Figure 2). Dynamic computed tomography of the lung showed thrombi lodged in the left and right pulmonary arteries propagate lower lobe artery (Figure 3). Echocardiogram showed enlarged right-sided chambers and mean pulmonary arterial pressure (PAP) 35 mmHg. With these findings, she was accepted as having massive thromboemboli, heparin infusion was stopped and thrombolytic therapy with streptokinase was given. She continued the therapy with heparin and warfarin with an overlap period of five days and international normalized ratio (INR) system of 2-3. The treatment was continued with peroral warfarin for six months.

The patient was investigated for the possibility of inherited hypercoagulable state. Normalized APC sensitivity ratio (SR) was 0.51; FV Leiden mutation was identified by polymerize chain reaction and she was found heterozygous for FV Leiden.

The level of protein C was normal at 120.6% and protein S was low 34% (70-128). Anti- cardiolipin antibodies

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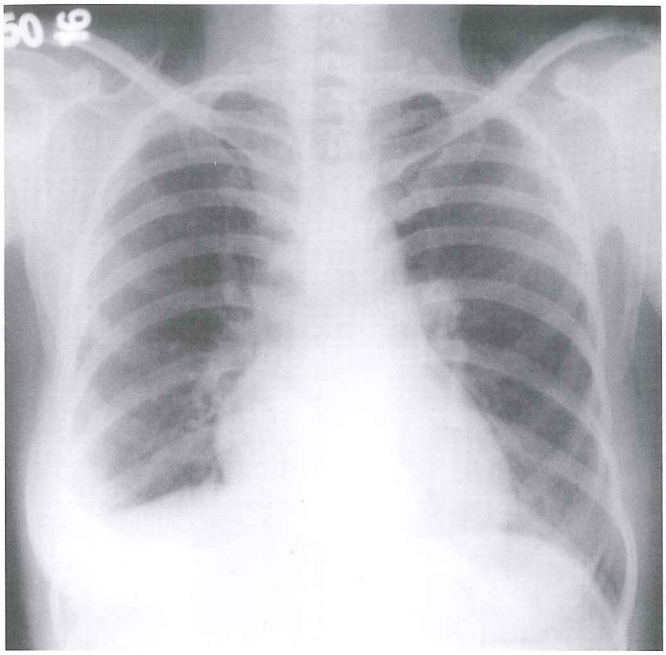

Figure 1

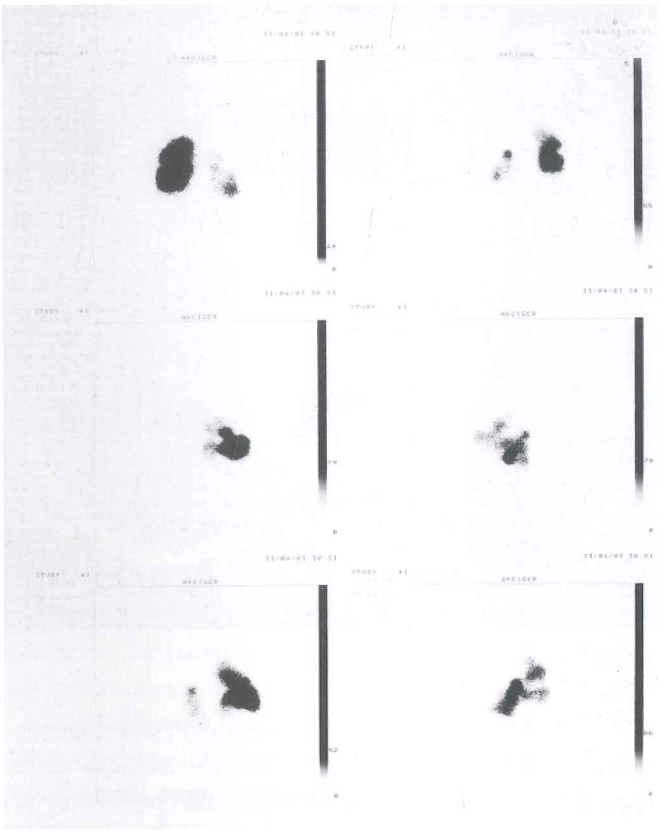

Figure 2

IgG and IgM, antinuclear antibody, SS-A/SS-B, anti-Sm, anti-U, and RNP were all negative.

The dynamic thorax computed tomography repeated at the second month of the anticoagulant therapy was normal.

DISCUSSION

This case demonstrates the increased risk of severe thromboembolic episode in patients with heterozygous APCR accompanied by another genetic defect, protein S deficiency.

APCR is the most prevalent cause of thrombosis, with an incidence of 20 to 50% [1]. The male to female ratio is 1:7. The defect is inherited as an autosomal dominant trait [1]. It is associated with the presence of a single point mutation in exon 10 of the FV gene predicting a Arg^{506} to Gln substitution. The resultant molecule (FV Leiden) has a reduced rate of inactivation by APC [2,3,7]. Identification of this mutation can be made by polymerase chain reaction based method. The presence of the mutation results in a reduction of the normalized APC SR [7]. There is a good correlation between coagulometric assay of APC and genotype for FV Leiden. Individuals heterozygous for FV Leiden show a nAPC-SR between 0.45 and 0.70 and increased risk for thrombosis (5-10 fold), whereas the homozygotes have nAPC-SR <0.45 and the risk is increased 50-100-fold [1,2-8].

Our patient showed a nAPC-SR 0.50 and she was heterozygous for FV Leiden.

Under physiologic conditions, procoagulant and anticoagulant mechanisms are balanced. Many plasma proteins are present to provide efficient hemostasis. Defects in the hemeostatic system may be associated with a hypercoagulable state. Deficiencies of protein C, protein S, and antithrombin are the most commonly identified congenital disorders for thrombosis, at rates of approximately 5-10% [1].

The risk of thrombosis is elevated by the concomitant presence of multiple factors. The risk is multiplied with a combination of factors, and major recurrent thromboembolic episodes can occur [1-6].

Acute massive pulmonary emboli can cause right ventricular dysfunction or failure. Echocardiographic evaluation is useful in determining the hemodynamic severity of pulmonary embolism. Kasper et al. [9] reported that dilatation of the right pulmonary artery and dilated right ventricle are the most common echocardiographic findings in patients with pulmonary embolism. Furthermore, the degree of right ventricular dysfunction would correlate with the extent of perfusion defects on the V/Q scan [10,11]. Helical thorax CT is highly sensitive up to 96% and specific (92%) when emboli were in the main lobar or segmental arteries [12].

Treatment with anticoagulants markedly reduces mortality; thrombolytic therapy is preferably used in hemodynamically unstable patients with massive emboli. Right ventricular dysfunction may improve markedly after the thrombolytic therapy [13].

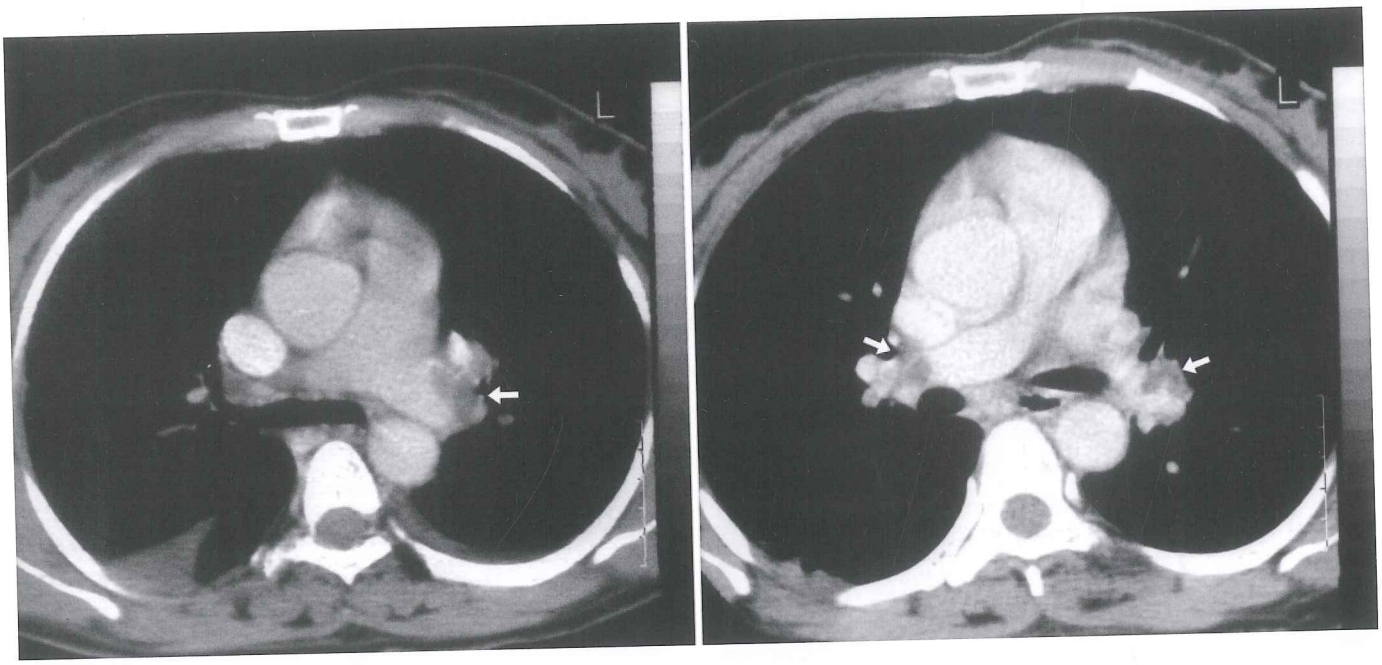

Figure 3

Our patient had massive thromboemboli with hemodynamic instability and acute cor pulmonale. Multiple perfusion defects and major thrombi in the main pulmonary arteries supported the diagnosis. She responded well to therapy with fibrinolytics and anticoagulants. We required her to use anticoagulants for six months. The duration of therapy can be discussed; since the risk is lifelong in such patients, lifelong therapy can also be considered.

REFERENCES

1. Rosendaal FR, Kaster T, Vondenbrouche JP, et al. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995;85:1504-8.
2. Bertina RM, Koelema BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64-7.
3. Greengard JS, Sun X, Xu X, et al. Activated protein C resistance caused by Arg506 to Gln mutation in factor V a. Lancet 1994;343:1361-2.
4. Dahlbäck B. New molecular insights into the genetics of thrombophilia. Resistance to activated protein C caused by Arg506 to Gln mutation in factor V as a pathogenetic risk factor. Thromb. Haemost 1995;74:139-48.
5. Saxena R, Mohanty S, Srivastava A, et al. Pathogenetic factors underlying juvenile deep vein thrombosis in Indians. Eur J Haematol 1999;63:26-8.
6. Saif MW, Volpe BT, Dailey M, et al. Life threatening pulmonary embolism in a factor V Leiden carrier on oral contraceptives: a case report. Conn Med 1997;61(6):333-7.
7. Dahlbäck B, Carrson M, Suensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. Proc Natl Acad Sci USA 1993;90:1004-8.
8. De-Ronde H, Bertina RM. Laboratory diagnosis of APC-resistance: a critical evaluation of the test and the development of diagnostic criteria. Thromb Haemost 1994;72:880-6.
9. Kasper W, Meinertz T, Henkel B, et al. Echocardiographic findings in patients with proved pulmonary embolism. Am Heart J 1986;112:1284-90.
10. Walge MV, Lee RT, Foldstein ML, et al. Prognostic significance of right ventricular hypokinesis and perfusion lung scan defects in pulmonary embolism. Am Heart J 1994;127:1371.
11. Ketai L, Wiest P, Wolf N, et al. Detection of pulmonary emboli and associated right heart dysfunction by combining ventilation perfusion lung scanning and xenon ventriculography. Clin Nucl Med 1997;22:817-20.
12. Goodman LR, Curtin JJ, Mewissen MW, et al. Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: helical CT vs angiography. Am J Roentgenol 1995;164:1369-74.
13. Come PC, Kim D, Parker JA, et al. Early reversal of right ventricular dysfunction in patients with acute pulmonary embolism after treatment with intravenous tissue plasminogen activator. J Am Coll Cardiol 1987;10:971-88.