High Factor IX Level With a Factor V 1691 G-A Mutation in a Case of Pulmonary Thromboembolism

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Abstract

Thrombophilic risk factors are accused in the pathogenesis of venous thromboembolism. Recently high levels of factor IX have been shown to increase the risk of deep venous thrombosis. We experienced a case of pulmonary thromboembolism (PTE), who had no risk factors for venous thromboembolism and was evaluated for inherited thrombophilic risk factors. She had normal Factor VIII level and no transition in the prothrombin gene but she was found to have high level of factor IX (173 IU/dl) and Factor V 1691 G-A mutation.
The patient was carrying two different thrombotic risk factors that were not reported before for the cause of PTE. The genetic basis of coagulopaty should be determined in all PTE patients without a significant risk factor..

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Introduction

Nearly all patients with pulmonary thromboembolism (PTE) are currently hospitalized or had a major surgery or serious illness. A number of circumstantial predisposing factors have been demonstrated for PTE. In addition to these circumstantial factors, genetic thrombotic abnormalities have been found in some of the subjects having venous thromboembolic diseases (1). Additionally high levels of factor IX have been shown to increase the risk of deep venous thrombosis recently (2). But its risk associated with PTE has not been investigated so far. Here we report a case of PTE who had no circumstantial risk factor but two different thrombotic abnormalities together: Factor V 1691 G-A mutation and high level of Factor IX.

Case Report

A 55-year-old woman was admitted to the emergency room with a sudden onset of pleuritic chest pain, dyspnea and haemoptysis. Her temperature was 36.6°C, pulse 132/min, respirations 40/min and blood pressure 120/70 mmHg. Her physical examination was normal, including the chest. PA chest radiograph showed an elevated left diaphragm with a basilar atelectasis on right lower lobe. Laboratory findings revealed a haematocrit of %36, white blood cell count of 7000/mm^3, platelet count of 192x10^3/mm^3.

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Biochemical tests were normal. She had a moderate hypoxemia (PO_2 65 mmHg) and respiratory alcalosis.

Pulmonary embolism was suspected and she underwent perfusion and ventilation (V/Q) scan of the lung. There were large segmental perfusion defects in upper lobe apical and lower lobe anterior segments, non-segmental perfusion defects in upper lobe posterior and anterior segments, middle lobe lateral and lower lobe superior segments in the right lung. In left she had large segmental perfusion defects in two of the lingular segments and in lower lobe superior, anterior and posterior segments. All defects were miss-matching ventilation abnormalities (Figure 1). A high probability V/Q scan was reported according to the criteria of Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) (3). She had no evidence of deep venous thrombosis (DVT) by doppler ultrasonography. Anticoagulation was initiated with standard heparin.

As she was a healthy person before with no other diseases, no prior surgery, no history of an episode of a DVT or PTE, and no recent significant risk factors for a thromboembolic disease (like recent surgery trauma, malign neoplasm, prolonged immobilisation, hormon replacement therapy) she was evaluated for inherited thrombophilic risk factors. DNA was extracted by conventional techniques. The G-to-A transition at nucleotide 1691 within the Factor V gene (Factor V Leiden) and the G-to-A transition at nucleotide position 20210 within the prothrombin gene locus (Factor II A^{20210}) were analysed according to previously reported techniques (4,5). Plasma levels of Factor VIII and IX were measured by a one stage-clotting assay with Factor VIII deficient plasma and Factor IX deficient plasma (Sigma Diagnostics, St. Louis, USA). Factor VIII level was normal and she had no transition in the Factor II gene but she was found to have Factor V Leiden (heterozygous) and high level of Factor IX [173 IU/dl (normal: 50-150 IU/dl)].

The patient was followed-up for a year but she neither had a recurrent disease nor developed a malignancy that could be an occult cause for venous thromboembolism (VTE).

Discussion

Genetic thrombotic risk factors are in current interest. High plasma level of Factor VIII is found to be a significant, independent and dose dependent risk factor for VTE (6). It is also shown to be a risk factor for recurrent VTE and severe PTE (7,8). Factor V Leiden and Factor II A^{20210} were found to be more associated with isolated DVT or DVT with a PTE than PTE alone (9). The risk of VTE is seven fold for heterozygous FVL carriers, where as the risk for homozygous carriers is approximately eighty-fold in comparison with non-carriers (10).

Though the role of high Factor IX level in PTE has not been investigated so far, a recent study of van Hylckama Vlieg et al. has demonstrated that individuals having high factor IX levels are associated with a 2-to-3 fold increased risk of experiencing DVT, a main form of venous thromboembolic disease. They also showed a trend towards a higher risk in females in comparison with males and a dose-response relationship between thrombosis and factor IX levels has been observed. Factor IX levels are increased with age (2). Our case was also a woman with relatively advanced age. She was a Factor V Leiden carrier and had high level of Factor IX, two different genetic thrombophilic risk factors together, that was not reported before for the cause of a thromboembolic event.

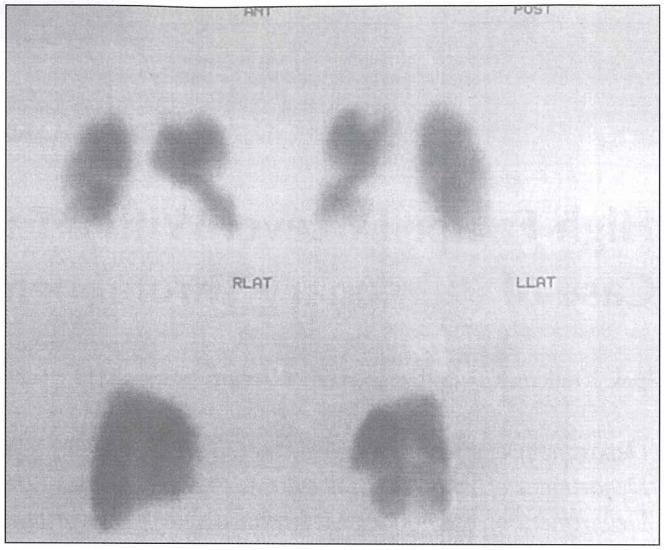

Figure 1. *Perfusion scan showing multiple segmental and non segmental perfusion defects.*

The interesting point of the case was; she had genetic risks for VTE but had no prior attack of VTE until age 55. We explained it by the fact that carriers of FVL often have mild thrombotic manifestations, rarely develop PE and may develop first thrombotic symptom at a relatively advanced age (10). Moreover, it is also known that additional genetic factors increase the risk of PTE when compared to single genetic abnormalities. The increased level of Factor IX by age and the presence of FVL caused first PTE episode in this woman at 55 years age.

We conclude that it is necessary to screen the genetic basis of coagulopathy in PTE patients with recurrent VTE, VTE in uncommon sites, who also have a history of PTE in his family and patients without a significant risk factor. Further investigations on the molecular basis of elevated factor IX levels and its role in the risk of PTE are also needed.

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