Serious Venous Thromboembolism, Heterozygous Factor V Leiden and Prothrombin G20210A Mutations in a Patient with Klinefelter Syndrome and Type 2 Diabetes

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Abstract

Klinefelter's syndrome (KS) is a common cause of man infertility characterized by small testes, gynecomastia and hypogonadism. Deep vein thrombosis and thromboembolic events are frequent in these patients. Hormone imbalance and co-existent mutations in the coagulation system may be the primary factors in this hypercoagulable state. The increased thromboembolic risk in hypogonadic men has been explained by hypofibrinolysis due to androgen deficiency. Regarding the association between KS and congenital and acquired thrombophilias, to date, only three cases have been. Here, we present the youngest KS case with pulmonary thromboembolism with the heterozygous mutations in factor V Leiden and prothrombin genes, as detected by further tests. He had the previous diagnosis of diabetes mellitus and body mass index was 30 kg/m². Our report discusses the prothrombotic state in KS patients, with other possible causes for the young presentation and the importance of necessary tests in emergency service admissions with embolism.

Key words: Klinefelter, XXY, factor V Leiden, prothrombin G20210A, diabetes, venous thromboembolism

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Introduction

Klinefelter syndrome (KS) which is first described by Klinefelter et al in 1942, is a common cause of man infertility characterized by small testes, gynecomastia, and hypogonadism with high levels of follicle stimulating hormone. It is genetically defined as the presence of extra X chromosome (47, XXY) with prevalence of one in 500 to 1,000 man (1, 2). Non-disjunction of the paternal sex chromosomes or maternal meiotic error is the defined reason for this chromosomal anomaly (2). Although the classical karyotype is 47, XXY there are some variant forms (like 48, XXYY or 48, XXXY) and mosaic forms (for example 46 XY/ 47 XXY mosaicism) (3, 4). Leydig cell dysfunction is manifested as small testes (<4 cm³), azospermia, and infertility in puberty and only approximately 25% of cases are diagnosed, most of them are diagnosed in adulthood (5, 6). Venous thromboembolism risk is reported to be moderately

increased in KS due to decreased androgen and increased estrogen levels. This can be partly explained by the reverse relationship between PAI-1 and testosterone levels (7, 8) and the prothrombotic effect of estrogens even at low levels (9). An analysis of 412 KS patients over a period of 1 to 20 years, revealed that the deep-vein thrombosis risk is 22.8 cases per 10,000 patient-years at risk, and the pulmonary embolism risk 16 cases/10,000 patient-years (10). Despite some rare thrombophilic disorders in this syndrome (11, 12) to date in the medical literature there are three cases of venous thromboembolism in KS. The case of Depaire-Duclos et al presented a 62 year-old case with heterozygous Factor V Leiden mutation (13). Ranganath and colleagues described a 60-year-old man with antiphospholipid syndrome (14) and Lapecorella et al discussed a 39-year-old man with heterozygous mutations in both factor V Leiden and prothrombin G20210A (15).

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Table 1. Coagulation Parameters and Genetic Analyses

Tests:	Results:	Normal range:
Factor VIII.....	150.0 %.....	50-150%
Protein C.....	120.0%.....	70-140 %
Total Protein S.....	98.7 %.....	55.0-160 %
Free Protein S.....	77.1 %.....	70-120 %
Antithrombin III.....	100%.....	70-121 %
Lupus anticoagulant.....	negative.....	negative.
Anticardiolipin IgG....	<2.0 GPL U/mL.....	<11.0 GPL U/mL
Anticardiolipin IgM...	<2.0 GPL U/mL.....	<10.0 GPL U/mL
PAI-1 plasma concentration.....		6.3 IU/mL
Factor V G1691A.....	Genotype: mutation in one allele/ Normal	
Prothrombin G20210A..	Genotype. mutation in one allele/ Normal	
MTHFR C677T.....	Genotype: Normal/ Normal	

Case presentation

A 26-year-old man patient came to our emergency department with sudden swelling and pain in his right leg. In his medical history, he had a diagnosis of Klinefelter's syndrome with 47 XXY karyotype and diabetes mellitus. He was not a smoker. There was no family history of venous thromboembolism. He had been using metformin 850 mg three times a day and rosiglitazone 4 mg/day with the diagnosis of type 2 diabetes mellitus for 5 years; his body mass index was 30 kg/m². Since he had a 38°C fever he was hospitalized. Within three hours of his hospitalization he developed a non-productive cough, severe pain localized to the right hemithorax, and hemoptysis. On Doppler ultrasonographic evaluation in his lower extremity there was acute and early subacute thrombosis in popliteal and distal crural veins, and chronic thrombosis in the superficial femoral vein, and insufficiency in the great saphenous vein below the knee level. In pulmonary tomography and angiography, the left main pulmonary artery, superior lobe and apico-posterior segment branches, lingual, lower lobe and lower lobe posterior-lateral basal segment branches, on right the lower lobe superior, posterior and lateral basal segmental arteries revealed filling defects relevant to pulmonary venous thromboembolism. D-dimer level on admission was 1,538 ng/mL (Normal range: 0-500 ng/mL), arterial blood pH was 7.46, pCO₂: 32.6 mmHg and pO₂: 81.0 mmHg with oxygen saturation of 97.4%. The patient had the diagnosis of deep vein thrombosis and pulmonary thromboembolism, and anti-

coagulant therapy was started with intravenous continuous infusion of non-fractionated heparin for the first 10 days alone, later oral anticoagulation was added targeting INR (International Normalized Ratio) values of between 2.0-3.0 and long-term anticoagulation with oral anticoagulants was planned.

His blood glucose level on admission was 135 mg/dL (two hours after lunch) (postprandial), and the glycemic control during his hospitalisation was good and his glycohemoglobin level was 6.2%.

Hormone and coagulation related laboratory analyses were performed before anticoagulation. His testosterone and free testosterone levels were lower and gonadotropins were increased as expected (Table 1). Coagulation test, plasma Factor VIII, protein C, protein S and antithrombin III levels, lupus anticoagulant, fibrinolytic parameters, and G1691A mutation for Factor V gene, G20210A mutation for prothrombin gene and C677T mutation for MTHFR (m-tetrahydrofolate reductase) gene were analyzed (Table 2). The patient was a heterozygote for both factor V G1691A with polymerase chain reaction and prothrombin G20210A mutations with restriction fragment length polymorphism analysis, without any mutation for MTHFR. Coagulation tests, Factor VIII, antithrombin, protein C, protein S activity and levels and fibrinolytic parameters were normal. Lupus anticoagulant was negative. PAI-1 level, analyzed with a chromogenic assay kit for plasminogen activator inhibitor type (Spectrolyse®/pL PAI), was within normal limits.

His lipid levels were also checked and his low density

Table 2. Hormonal Tests

Tests:	Results	Normal range for men:
Testosterone.....	...1.20	2.80-8.00 ng/dL
Free testosterone.....	...2.80.....	5.60-19 pg/dL
FSH.....	...4.41.....	0.50-2.41U/L
LH.....	17.....	1.00-11.40mIU/mL

FSH: Follicle stimulating hormone, LH: Luteinizing hormone.

lipoprotein (LDL) cholesterol level was 98 mg/dL, high density lipoprotein cholesterol (HDL) was 52 mg/dL and triglyceride was 111 mg/dL, indicating the absence of any type of dyslipidemia. Transthoracic echocardiography revealed neither thrombus formation, nor dilatation of any heart chambers, without valvulopathy.

Discussion

Patients with Klinefelter syndrome are observed to be more likely to have problems related to the coagulation system, leading to thromboembolism or leg ulcers (10). The most common hereditary disorders of coagulation are deficiencies of antithrombin III, protein C, protein S, and mutations in factor V Leiden, but also dysfibrinogenemia, increased plasminogen activator inhibitor levels, and deficiencies of tissue plasminogen activator or heparin cofactor II, homocystinuria may be found (16). However, the underlying mechanisms are not clearly explained, it is possible to theorize that increased platelet aggregability and defective fibrinolysis due to hormone imbalance or accompanying genetic mutations are responsible (17); this relationship was already reported twenty years ago (18). Elevated levels of PAI-1 are thought to be responsible in most KS patients with leg ulcers, but later studies have shown that it may only be partly responsible and there are likely some additional unknown causes (19, 20). In the present case PAI-1 levels were normal, hyperestrogenism, hyperhomocysteinemia and hypofibrinolysis were not present. Together with detected mutations, these findings also support the role of genetic mutations in severe thromboembolism in our case.

The present case is similar to that presented by Lapecorella et al, with the same heterozygous mutations in factor V Leiden and prothrombin and these mutations explain the hypercoagulant state in these two cases (15). The present case is 15 years younger than the other case with the same presentation. The co-existence of diabetes may be the reason of earlier massive embolism, although the glycemic control of the patient was favourable.

Diabetes mellitus is suggested to be associated with coagulation system changes, such as impaired fibrinolysis, hy-

perlipidemia, increased platelet reactivity and different peroxisome proliferator-activated receptor (PPAR) polymorphisms (21) may lead to thrombogenic tendency. Although diabetes with hyperosmolar state and ketoacidosis were reported with an increased risk of venous embolism (22, 23), in the study of Petrauskiene et al, 302 patients were evaluated and the diabetic patients revealed a two-fold higher risk for venous thromboembolism even though they did not have any acute hyperosmolar or ketoacidosis states (24). But the data in the literature is conflicting, for example in the prospective evaluation of 5,522 patients of HOPE-2 patients including 2,209 diabetics, none of the metabolic syndrome components were found to be related with venous thromboembolism risk (25). Obesity is another important risk factor for venous thromboembolism (26). Circulating procoagulant microparticles which are the fragments from the plasma membrane have been claimed to be responsible for the increased venous embolism risk (27).

Thus, according to recent studies, atherosclerosis and venous thromboembolism share some common risk factors such as age, diabetes, obesity and hyperlipidemia, metabolic syndrome, the association and its clinical importance is not clear (28). Also in the study of Linnemann et al, diabetes, obesity, smoking and hypercholesterolemia were not found to be related to venous thromboembolism recurrence (29). But in the last meta-analysis, venous embolism was increased 1.42 times in diabetes and 2.33 in obesity (30). Considering the present case with a shorter duration of diabetes and acceptable glycemic control, the presence of diabetes may be a weaker factor but obesity may contribute more to his procoagulant state.

The incidence of metabolic syndrome and diabetes is high in KS patients (31) and it is a frequent cause of mortality and morbidity (32). Hypogonadism may be the cause of unfavourable change in body composition and the imbalance between testosterone and its metabolite dihydrotestosterone may cause insulin resistance (33).

In the medical literature there is another young case of admission of to the emergency department with pulmonary embolism, having the diagnosis of pulmonary embolism together with patent foramen ovale thrombosis (34); they sug-

gested the use of transesophageal echocardiography (TEE) for cardiovascularly unstable patients and complex cases. In the present case echocardiography was performed in transthoracic way, and on physical examination cardiac evaluation was normal without any murmur, and cardiovascular parameters were stable. Thus TEE was not needed. But in KS patients with unstable vital signs, the high possibility of valvulopathies and intracardiac thrombi should be considered (34, 35).

It is known that the co-existence of mutations in factor V Leiden and prothrombin cause a higher risk of recurrent thromboembolic events when compared with the carriers of each mutation alone (36). The prevalence of MTHFR

C677T mutation is also frequent with differing degrees in different populations and the presence of mutations in all three (factor V Leiden, prothrombin and MTHFR) is not low (37, 38); the prevalence of prothrombin G20210A and Factor V Leiden mutations in white Europeans are 1-3% and 3-7%, respectively (39). Thus, it should be investigated together with other mutations in hypercoagulable patients.

In conclusion, with the presentation of this patient we would like to emphasize the hypercoagulable state in the KS patient group, and that lifelong oral anticoagulant therapy should be planned in thromboembolic patients who are carriers of factor V Leiden and prothrombin gene mutations, as in the present patient.

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