Pulmonary Thromboembolism in Klinefelter's Syndrome Patient with Deficient of Protein C

Protein C Eksikliği ile Birlikte olan Klinefelter Sendromunda Pulmoner Tromboemboli Olgusu

Klinefelter Sendromunda Pulmoner Tromboemboli Olgusu / Pulmonary Thromboembolism with Klinefelter's Syndrome

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Özet

Klinefelter sendromu (KS) bir veya daha fazla X kromozomu nedeniyle gözlenen yaygın bir genetik bozukluktur . KS böyle derin ven trombozu ve pulmoner emboli gibi venöz tromboembolik olaylar için artmış bir risk oluşturmaktadır . KS'u nedeniyle hormonal dengesizlik ve bir veya daha fazla trombofilik faktörler hiperkoagulibilite eğilimi artmıştır. Bu nedenle, Klinefelter sendromunda venöz tromboemboli gibi bir tıbbi geçmişi olan hastalarda göğüs bilgisayarlı tomografi (BT) görüntülemesi ve en az altı aylık bir süre için oral antikoagulan tedavi gereklidir. Klinefelter sendromu tanısı alan 21 yaşındaki erkek hasta, 2 ay boyunca süren sol alt ekstremite ağrısı primer şikayeti ile hastanemiz acil servisine başvurdu. Derin ven trombozu (DVT) venöz doppler ultrasonuyla pulmoner tromboemboli ise toraks BT görüntüleriyle tespit edildi. Antikoagulan tedavisi sonrasında hastanın semptomları iyileşti. KS olan hastalar trombofiliye yatkınlık olduğu için mutlaka endokrinolojik testler veya görüntüleme yöntemleri ile akut trombüs açısından değerlendirilmelidirler.

Anahtar Kelimeler

Klinefelter Sendromu; Protein C Eksikliği; Pulmoner Emboli

Abstract

Klinefelter syndrome (KS) is a common genetic disorder caused by one or more supernumerary X chromosomes. KS poses an increased risk for venous thromboembolic events such as deep venous thrombosis and pulmonary embolism. Klinefelter syndrome is prone to hypercoagulability due to hormonal imbalance and one or more inherited thrombophilic factors. Therefore, patients with KS having a medical history of venous thromboembolism require chest computed tomographic (CT) images and oral anticoagulation therapy for a period of at least six months. A 21 year old, male patient diagnosed with Klinefelter syndrome was presented to the emergency department of our hospital with primary complaints of left lower extremity pain lasting for 2 months. Deep venous thromboembosis (DVT) was diagnosed via venous doppler ultrasound and pulmonary thromboembolism in his chest CT images. Following anticoagulation treatment, his symptoms recovered. An endocrinologic test should be ordered in patients having klinefelter syndrome with a medical or familial history of venous thromboembolism as well as additional assessment of innate or acquired thrombophilia should be made.

Keywords

Klinefelter Syndrome; Protein C Deficiency; Pulmonary Embolism

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Introduction

Klinefelter syndrome is the most common congenital abnormality leading to primary hypogonadism, developing in approximately one per thousand (1:1000) live male births [1]. Variation of 48,XXYY occurs in 1 in between 18,000 to 50,000 male births [2]. This syndrome has a numerical chromosome abnormality in males, characterized by the presence of one or more extra X chromosomes [3]. KS is also associated with an increased risk for venous thromboembolic events (VTEs) such as deep venous thrombosis (DVT) and pulmonary embolism (PE) . Recent studies report the prevalence of KS as 1 : 640 [4,5], and this makes KS the most prevalent aneuploidy in males and also the most common cause of male infertility. Despite the underlying mechanism remains unclear, it is believed to be related to a hypogonadism syndrome causing an increased synthesis and activity of plasminogen activator inhibitor-1 (PAI-1) and thus a decreased fibrinolytic activity [6]. It might be hypothesized that KS patients have also a higher risk to develop chronic thromboembolism and chronic thromboembolic pulmonary hypertension (CTEPH) [7]. Herein, we presented a young male patient with KS who also had venous thrombosis, pulmonary thromboembolism and, protein C deficiency.

Case Report

A twenty one year-old male patient, diagnosed with KS (48, XXYY) during the sterility test, was presented to the emergency department of our hospital's with the primary complaints of left lower extremity pain which lasted 6 months prior to admission. His body temperature was 37.1°C . His blood pressure, pulse and respiration were 105/65 mm Hg, 115/minute and 22/minute, respectively at the time of admission. Heart sounds yielded rapid pulse and no murmur was observed. Crackles were heard in both lower lungs on auscultation of the chest. On the electrocardiography, ST-depression was observed in the V3, V4 and V5 areas but S1Q3T3 pattern was not observed. Increased right ventricular size and decreased right ventricular function were observed in the echocardiography. WBC was found as 9810/μL, Hb 15.7 g/dL and platelet 17700 K/mL on the peripheral blood test. Finding of inflammation with high sensitivity C-reactive protein 3.6 mg/dL (n:0-0.5) was revealed in an immunochemical serologic test. Blood urea nitrogen was found as 10.75 mg/dL, creatinine 1.0 mg/dL. The level of D-dimer was measured to be high at 8.98 ug FEU/ml (n:0-0.5). While the patient was on O2 mask 4 L, arterial blood gas analysis resulted in hypoxemia with pH 7.51, PCO2 26.3 mm Hg, PO2 71.4 mm Hg, HCO3 20.4 mmol/L and O2 saturation of 92%. Protein C of the patient 49% (n:70 – 140%), protrombin (FII) polimorfism mutant, protein S 124% (n: 60 – 130%) were determined in Table 1.

Table 1. Coagulation parameters and genetic analyses

Tests	Results	Normal Range
Protein C Aktivitesi	49%	70-140
Protein S Aktivitesi	124%	60-130
Faktör V leiden (G16917=R506Q)	Gecotype	Normal/Normal
Faktör II (Protrombin) G20210A	Mutant	Normal

A contrast enhanced chest computed tomography was ordered with a suspicion of possible pulmonary thromboembolism, which revealed multiple thromboembolism in the main, lobar, segmental and subsegmental pulmonary arteries of both lungs (Fig. 1). Despite an O2 mask of 8 L O2 saturation of the patient

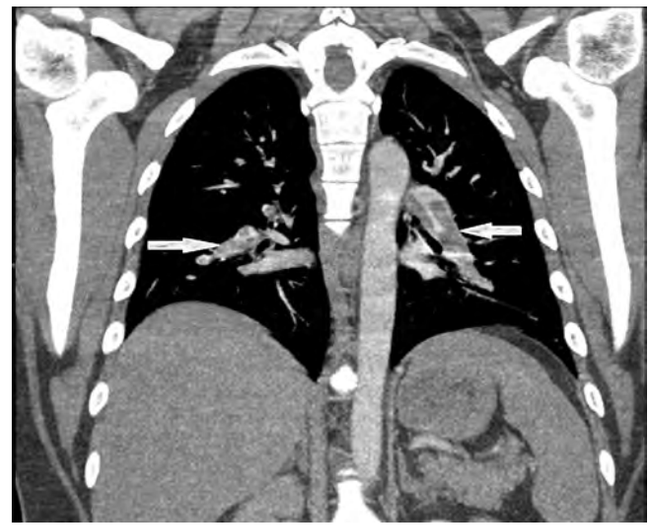


Figure 1. Pretreatment coronal computed tomography image of the patient.

dropped to 88-90%. On the persistent hypotension of 88/53mm Hg was observed, despite hemodynamic support, thrombolytic therapy (Alteplase: 100 mg over 2 hours) was administered. Venous doppler ultrasound performed revealed acute - subacute term thrombosis in the left external iliac vein, superficial femoral vein, popliteal vein, common femoral vein, profound femoral vein, and chronic term thrombosis in the left trifurcation. The patient was administered anticoagulation therapy with low molecular weight heparin (enoxaparin: 60 mg subcutaneously every 12 hours for 7 days) and warfarin.

Having observed venous thromboembolism at a young age, a screening test for immunologic diseases was performed to set the differential diagnosis of antiphospholipid antibody syndrome. All of the following were found to be negative: the findings of complement levels (C3, C4), antibody to anti-double-stranded DNA antinuclear antibody (ANA), anticardiolipin antibody of immunoglobulin M and G, as well as lupus anticoagulant and venereal disease research laboratory outcome. The patient was put on warfarin for anticoagulation therapy after he was discharged.

Discussion

There is an increased incidence of venous thromboembolism in patients having Klinefelter syndrome. In their series of 412 patients having Klinefelter syndrome, Campbell and Price reported an increased incidence of DVT and pulmonary embolism, observed over periods ranging from 1 to 20 years [6]. A possible explanation was the effects of androgens on hemostasis which was reported in two consecutive studies and then emphasized by Winkler in his review [8-10]. According to these findings, hypogonadism in males is related to reduced fibrinolytic activity through the increased levels of plasminogen activator inhibitor-1 (PAI-1), where plasma levels show an inverse relationship with testosterone concentrations. In our case, the diagnosis was established with venous doppler ultrasound for acute - subacute term thrombosis in the left external iliac vein, superficial femoral vein, common femoral vein, popliteal vein,

profound femoral vein, and chronic term thrombosis in the left trifurcation.

In conclusion, an endocrinologic test should be ordered in patients having klinefelter syndrome with a medical or familial history of venous thromboembolism as well as additional assessment of innate or acquired thrombophilia should be made. It seems that further studies on understanding of pathogenesis of venous thromboembolism in cases of KS are needed in the future. We consider that a long-term oral anticoagulation therapy is necessary for the treatment of thrombophilic conditions. We believe that whole body screening would decrease mortality in these patients if acute thrombosis is developed in these patients.

Competing interests

The authors declare that they have no competing interests.

References

1. Schwartz ID, Root AW. The Klinefelter syndrome of testicular dysgenesis. Endocrinol Metab Clin North Am. 1991;20:153-163.
2. Linden, M.G; Bender, B.G; Robinson, A. (1995). Sex chromosome tetrasomy and pentasomy. Pediatrics 96 (4Ptl):672-682.
3. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab. 2003;88:622-626.
4. Herlihy AS, Halliday JL, Cock ML, McLachlan RI. The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. Medical Journal of Australia.2011;194:24-28.
5. Morris JK, Alberman E, Scott C, Jacobs P. Is the prevalence of Klinefelter syndrome increasing? European Journal of Human Genetics. 2008;16:163-170.
6. Byung-Soo Kang, Deok-Kyu Cho, Won-Jun Koh, Seung-Hoon Yoo, Ki-Bum Won, Yun-Hyeong Cho, et al. A case of severe pulmonary thromboembolism in a young male with Klinefelter syndrome. Korean Circ J. 2012 August; 42(8): 562–564
7. Bonderman D, Wilkens H, Wakounig S, H-J. Schafers HJ, Jansa P, Lindnere J et al. Risk factors for chronic thromboembolic pulmonary hypertension. European Respiratory Journal. 2009;33:325-331.
8. Bennet A, Sie´ P, Caron P, Boneu B, Bazex J, Pontonnier F. Plasma fibrinolytic activity in a group of hypogonadic men.Scand J Clin Lab Invest. 1987;47:23-27.
9. Caron P, Bennet A, Camare R, Louvet JP, Boneu B, Sié P. Plasminogen activator inhibitor in plasma is related to testosterone in men. Metabolism. 1989;38:1010-1015.
10.Winkler UH. Effects of androgens on haemostasis. Maturitas. 1996;24:147-155.

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