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Rare Vasculo-pathologies in a Case with Klinefelter Syndrome: Pulmonary Embolism, Right Aortic Arch and Aberrant Subclavian Artery

Klinefelter Sendromlu Bir Olguda Nadir Vasküler Patolojiler: Pulmoner Emboli, Sağ Aortik Ark ve Aberran Subklaviyen Arter

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Abstract

Klinefelter syndrome (KS) is a sex chromosome abnormality characterized by a 47, XXY karyotype. While the exact cause of the condition remains unknown, the incidence of pulmonary embolism (PE) is higher in KS patients. Several hypotheses have been put forward to explain this condition, including hypogonadism, which leads to hormonal imbalances due to low testosterone levels and an increased estrogen-to-testosterone ratio, as well as testosterone deficiency and the associated adverse effects on the vascular endothelium. A number of congenital cardiovascular anomalies have been reported in the literature in patients with KS. That said, no cases involving a right-sided aortic arch and aberrant subclavian artery have been reported to date. We present here the case of a patient who was admitted to our clinic with a PE after being diagnosed with KS, and with a right aortic arch and an aberrant subclavian artery anomaly.

Keywords: *Aberrant Subclavian Artery, Klinefelter Syndrome, Pulmonary Embolism, Right-Sided Aortic Arch.*

Öz

Klinefelter sendromu (KS), bir seks kromozomu anomalisi olup, çoğunlukla 47, XXY karyotipi ile karakterizedir. Her ne kadar kesin olarak sebebi bilinmese de Pulmoner Emboli (PE) insidansının KS'li olgularda arttığı bilinmektedir. KS'li olgularda hipogonadizm sonucu serum testosteron düzeyleri yetersiz seviyelerde seyretmesinin bir hormonal dengesizliğe yol açması, östrojen/testosteron oranı artması, testosteron eksikliğinin, damar endoteli üzerinde olumsuz etkilere yol açması gibi birden fazla hipotez ile durum açıklanmaya çalışılmaktadır. Yine KS'li olgularda şu ana kadar literatürde bildirilen çok sayıda konjenital kardiyovasküler anomali var iken Sağ Aortik Ark ve Aberran Subklavian Arter anomalisi bildirilmemiştir. Burada, KS tanısı aldıktan sonra PE teşhisi ile kliniğimize yatan ve bu sırada Sağ Aortik Ark ve Abberan Subklavian Arter anomalisi tespit edilen bir olgu paylaşılmıştır.

Anahtar Kelimeler: *Abberan Subklavian Arter, Klinefelter Sendromu, Pulmoner Emboli, Sağ Aortik Ark.*

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Klinefelter syndrome (KS) is the most common sex chromosome abnormality in males and is most frequently characterized by a 47, XXY karyotype. The most common clinical findings include reduced testicular volume, hypogonadism, infertility, gynecomastia and tall stature. During adolescence, many patients experience subnormal serum testosterone levels as a result of hypogonadism, which can lead to such symptoms as decreased muscle mass, low bone mineral density, fatigue, loss of libido and depression (1).

The most significant risk factors for PE include a history of venous thromboembolism, lower extremity fractures, hip or knee arthroplasty, major trauma, recent hospitalization within the past 3 months due to heart failure or atrial fibrillation, recent myocardial infarction and spinal cord injury (2). Although the exact cause is not known, KS patients have a predisposition to PE. The increased procoagulant PAI-1 (plasminogen activator inhibitor-1) levels in KS patients associated with their genetic structure and low testosterone levels significantly increase the risk of PE. The risk of venous thromboembolic events is approximately three to six times higher in KS patients than in the general population (3). We present here the case of a 27-year-old patient with Klinefelter syndrome (KS) who was newly diagnosed with pulmonary embolism (PE), along with pectus excavatum, a right-sided aortic arch and an aberrant subclavian artery. We introduce this case to the literature, given the rarity of the coexistence of PE alongside these vascular anomalies in association with KS.

CASE

A 27-year-old male patient who had undergone a right radical orchiectomy 1 month earlier and was diagnosed with KS was admitted to the emergency department following the sudden onset of right-sided chest pain, shortness of breath and palpitations. On inspection, his vital signs were within normal ranges, while a physical examination revealed the patient to have a tall and thin phenotype, measuring 185 centimeters in height and 70 kilograms in weight, with a calculated body mass index (BMI) of 20.45. The patient was also noted to have a pectus excavatum deformity (PED) (Figure 1). Auscultation revealed crackles at the base of the right lung, and a posteroanterior chest radiograph showed an oligemic appearance in the right hemithorax and a right-sided aortic arch (Figure 2). Thoracic computed tomography angiography (CTA) revealed a filling defect consistent with pulmonary embolism (PE) in a segmental branch of the right lung, as well as a ground-glass opacity in the right lower lobe that was consistent with infarction.

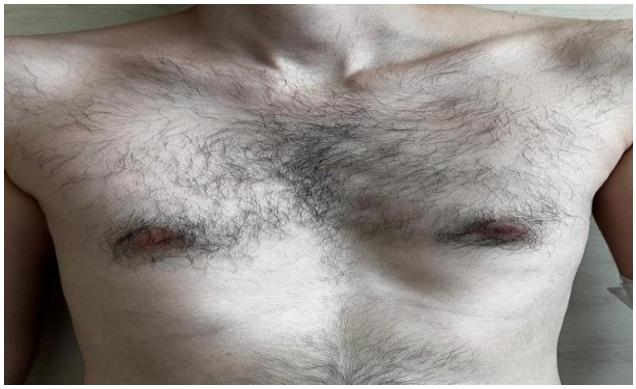

Figure 1: Pectus excavatum deformity observed phenotypically in the patient.

Aside from the pectus excavatum deformity (PED), the patient was also noted to have a right-sided aortic arch variation (RAAV) and an aberrant subclavian artery (ASA) (Figures 3 and 4). Laboratory tests (Table 1) revealed elevated serum C-reactive protein (CRP), D-dimer and mildly increased estradiol (E2) levels. No other abnormalities were detected (CRP: 37.4, D-Dimer: 0.87, E2: 43.9). Further anamnesis revealed that the patient had been diagnosed with Klinefelter syndrome (KS) following genetic testing conducted due to a decrease in testicular size and the presence of a palpable lesion in the testis 1 month prior (Figure 5). The histopathological report reported the orchiectomy specimen to be a "Benign Leydig cell tumor". Based on these findings (KS, PE, PED, AAV, ASA), the patient was admitted to the Chest Diseases Department for further evaluation and treatment. The PE severity index (PESI) score was 37, corresponding to class 1. The patient was started on low molecular weight heparin treatment at a therapeutic dose, a medical genetics consultation was requested and a thrombophilia panel was sent. Bilateral lower extremity venous Doppler ultrasonography was reported as normal, and echocardiography revealed no pathology other than mild mitral regurgitation. Cardiac enzymes (troponin and BNP) were normal. The patient was considered low-risk for PE and discharged with oral anticoagulation and coagulation profile follow-up. Informed consent for this report was obtained from the patient.

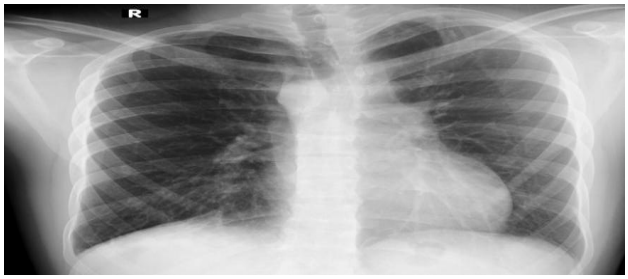

Figure 2: Posteroanterior chest radiograph taken at presentation showing increased aeration (oligemic appearance) in the right hemithorax and a right-sided aortic arch.

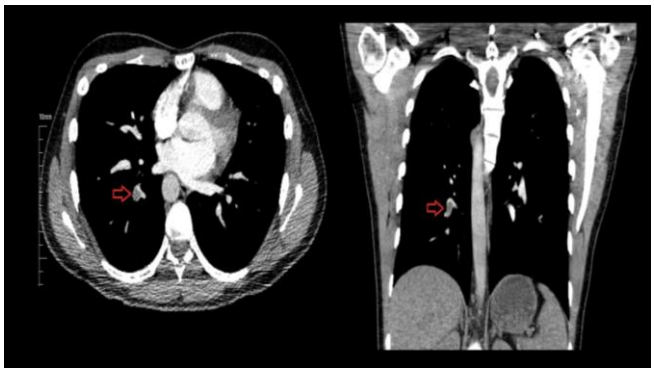

Figure 3: Thoracic computed tomography angiography (CTA) of the patient revealing a filling defect compatible with PE in a segmental branch of the right lung

DISCUSSION

Described here is the case of a 27-year-old male with Klinefelter syndrome (KS) who was diagnosed with pulmonary embolism (PE) in the absence of any known major risk factors. We present this case to the literature to highlight the increased predisposition to PE in individuals with KS, as well as the potential for accompanying anatomical anomalies. The numerous risk factors for pulmonary embolism (PE) that have been identified are generally categorized into three main groups, representing major, intermediate or minor risks (Table 2) (4). Major risk factors, such as significant trauma, prior PE and lower extremity fractures, are associated with up to a 10-fold increase in PE risk. Hormone replacement therapy, oral contraceptive use and chemotherapy, on the other hand, are classified as intermediate risk factors and have been reported to increase the risk 2–9-fold. It has long been known that estrogen increases the risk of venous thromboembolism, and consequently PE, by elevating procoagulant factors, suppressing the natural anticoagulant systems and reducing fibrinolytic activity (5). Patients with KS are more likely to develop pulmonary embolism (PE) than the general population, and most are under the age of 30 years. Studies have also reported an increased incidence of PE in individuals with KS, which is, in turn, considered a persistent risk factor for recurrent PE (6-8). Many hypotheses have been put forward to explain the predisposition to PE of patients with KS (high homocysteine levels, antithrombin III, protein C and S deficiency, vascular abnormalities, decreased muscle mass and decreased physical activity making venous return difficult, genetic variations on the X chromosome affecting the F8 and F9 genes and coagulation pathways, etc.). The most widely accepted hypothesis suggests that elevated PAI-1 promotes a prothrombotic state by inhibiting the tissue plasminogen activators, thereby reducing the conversion of plasminogen to plasmin and impairing fibrinolytic mechanisms (9). Studies have also shown that men with KS exhibit relative hyperestrogenism, with higher estradiol/testosterone ratios when compared to controls (10). This hyperestrogenic state may play a role in the development of thromboembolic disease in KS patients, as estrogen can alter the levels of procoagulant and anticoagulant proteins, particularly in the presence of inherited thrombophilia (9,11). It has been reported in the literature that testosterone replacement therapy can increase the risk of thrombosis, especially in young men (12). However, the fact that the presented case had never received testosterone therapy suggests that the pathogenesis of KS-related thrombosis is much more complex, and that the risk is higher in the early period. A review of previous studies of vascular anomalies in KS reveals reports of both anatomical anomalies (such as portal vein aneurysms and cerebellar arteriovenous malformations) and functional vascular abnormalities (including arterial narrowing and endothelial dysfunction). However, to the best of our knowledge, there have to date been no studies reporting an association between congenital anomalies such as pectus excavatum (PED), right-sided aortic arch (RAAV) or aberrant subclavian artery (ASA) and KS (13–16). A review article by Calogero et al. (17) listed a number of cardiovascular anomalies observed in patients with KS, including mitral valve prolapse, acute mitral regurgitation, bilateral internal carotid artery hypoplasia, bilateral vertebral artery dilatation, hypertrophic cardiomyopathy, atrial and ventricular septal defects, partial anomalous pulmonary venous return, pulmonary hypertension, tricuspid regurgitation and patent ductus arteriosus.

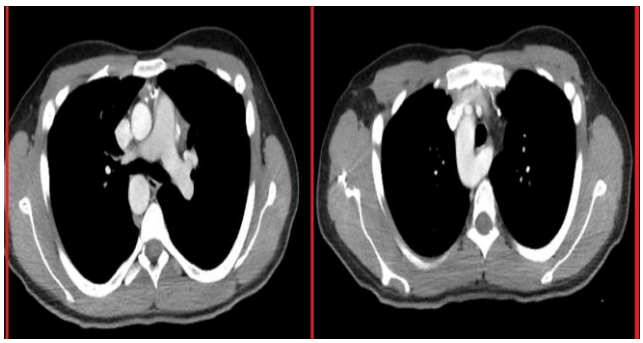

Figure 4: Thoracic computed tomography angiography (CTA) showing a right-sided aortic arch variation and an aberrant subclavian artery

Table 1: Laboratory values of the case

Parameter	Result	Reference	Parameter	Result	Reference
WBC (103uL)	7	4 -10	CRP (mg/L)	37.4	0 – 5
Hemoglobin (g/dL)	12.7	12-16	Procalcitonin (μg/L)	0.063	<0,5
Hematocrit (%)	38	36 – 47	D-dimer	0.87	<0,50
Urea (mg/dL)	16	16.6 - 48.5	Glucose (mg/dL)	110	74 – 106
Kreatinin (mg/dL)	0.85	0.5 - 0.9	Total Bilirubin (mg/dL)	0.95	0 - 1.2
ALT (U/L)	13	0 – 33	Sodium (mmol/L)	142	135-145
AST (U/L)	11	0 – 32	Potassium (mmol/L)	3.8	3,1 - 5,1
Estradiol E2 (ng/L)	43.9	11.3-43.2	Progesterone (ng/mL)	0.55	0.15-1.0

ALT: Alanin Amino Transferaz, AST: Aspartat Amino Transferaz, CRP: Serum Reaktif Protein, LDH: Laktat Dehidrogenaz, WBC: White Blood Cell

Gerretsen et al. (18) reported a case of KS with vascular anomalies similar to ours, but without involvement of a right-sided aortic arch (RAAV) or an aberrant subclavian artery (ASA). Their described a 14-month-old pediatric patient with Down syndrome (DS) and KS associated with a double aortic arch, which was considered a case of double aneuploidy. However, the authors did not explain the possible pathophysiological mechanisms of the double aortic arch, stating only that it may be incidental or associated with DS. It is unclear whether the presence of cardiovascular anomalies in cases with KS can influence the development of PE. We believe, however, that a detailed anatomical examination should be performed in patients with KS. Although an association between PE and KS was considered in our case, the history of surgery 1 month prior should not be ignored. The development of PE in postoperative patients is known to occur predominantly in those who do not receive prophylactic treatment for the condition, and typically within the first week following surgery. Additionally, postoperative PE is more common in patients with obesity, those who have undergone cancer-related surgery, and those with a history of cerebrovascular disease or prior thromboembolic events. In our case, the absence of these risk factors, the diagnosis of PE 1 month after surgery and the onset of symptoms (sudden chest pain, dyspnea, palpitations) on the day of diagnosis all reduce the likelihood of the PE being related to the surgery (19). In conclusion, this case report concurs with previous studies in the literature reporting an association between PE and KS, and suggests that this association may be present even at an early age and close to diagnosis. The importance of a comprehensive radiological evaluation for pulmonary vascular pathologies such as PE as well as rare accompanying anatomic vascular anomalies in KS should thus be emphasized.

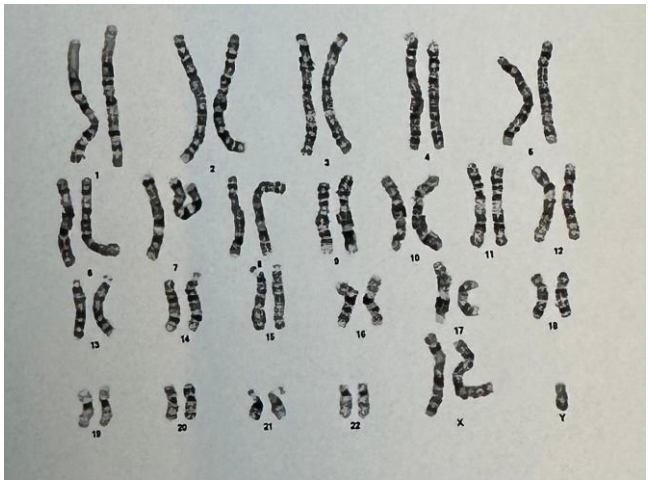

Figure 5: Genetic analysis result of the patient confirming the diagnosis of Klinefelter syndrome (47, XXY karyotype)

Table 2: Risk factors for Pulmonary Embolism (*)

Major risk factors	Moderate risk factors	Minor risk factors
-Fracture of the lower extremity -Hospitalization due to heart failure (HF), atrial fibrillation (AF), or flutter (within the last 3 months) -Hip or knee replacement surgery -Major trauma -Myocardial infarction (MI) within the last 3 months -History of venous thromboembolism (VTE) -Spinal cord injury	-Arthroscopic knee surgery -Autoimmune diseases -Blood transfusion -CVP and IV catheters -Chemotherapy -CHF or respiratory failure -Erythropoiesis-stimulating agents -Hormone replacement therapy -In vitro fertilization -Oral contraceptives, Postpartum treatment -Infections (Pneumonia, UTI, HIV) -Inflammatory bowel disease -Cancer diagnosis -Paralytic stroke -Superficial vein thrombosis -Thrombophilia	->3 days bed rest -DM -Arterial hypertension -İmmobilization -Advanced age -Laparoscopic surgery -Obesity -Pregnancy -Varicose veins -Venous catheters
(>10-fold risk)	**(2-9-fold risk)**	**(<2-fold risk)**

AF: atrial fibrillation , CVP: Central venous pressure catheters, DM: Diabetes mellitus, CHF: Congestive Heart Failure, KY: Kalp Yetmezliği, IV: İntravenous, UTI: Urinary Tract İnceftion, MI: Myocardial infarction, VTE: venous thromboembolism

(*) Adapted from reference number 4.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - A.Y., C.D., Z.N.K., G.S.Y.; Planning and Design - A.Y., C.D., Z.N.K., G.S.Y.; Supervision - A.Y., C.D., Z.N.K., G.S.Y.; Funding - Z.N.K.,C.D.; Materials - Z.N.K., G.S.Y.; Data Collection and/or Processing - A.Y., C.D.; Analysis and/or Interpretation - A.Y.,G.S.Y.; Literature Review - C.D.,G.S.Y.; Writing - A.Y., C.D.; Critical Review - A.Y., C.D.

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