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Severe Arterial Thrombophilia Associated With a Homozygous MTHFR Gene Mutation (A1298C) in a Young Man With Klinefelter Syndrome

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Klinefelter syndrome (KS) is the most common sex chromosome disorder in men. It may be associated with an increased risk for venous thrombosis and thromboembolism, which is partially explained by hypofibrinolysis due to androgen deficiency. Additional genetic or acquired thrombophilic states have been shown in KS patients complicated with venous thrombosis as isolated case reports. Arterial thrombotic events had not been previously reported in KS. In this study, a young man with KS who developed acute arterial thrombosis during testosterone replacement therapy is presented. He was homozygous for the A1298C mutation of the methylenetetrahydrofolate reductase (MTHFR) gene.

Keywords: Klinefelter syndrome; arterial thrombophilia; MTHFR gene mutation

Klinefelter syndrome (KS) is the most common sex chromosome disorder in men, affecting roughly 1 in 400–600 men throughout all ethnic groups.[1-3] KS can cause impairment of both spermatogenesis and testosterone production. The majority of patients with KS have decreased total testosterone levels. Likewise, KS patients presenting with normal total testosterone levels may actually have decreased free testosterone, because sex hormone binding globulin levels are elevated in KS.[1-3] Accordingly, the clinical features of the disease usually appear after puberty and include bilateral painless gynecomastia, variable degree of eunuchoidism, small firm testes with hyalinization of the seminiferous tubules, elevated gonadotropins, and azospermia. The clinical diagnosis is confirmed by chromosomal analysis of either peripheral blood leukocytes or tissue, which usually reveals a 47, XXY genotype. In rare cases, additional X chromosomes may be present, or the individual may be mosaic (46, XY/47, XXY).[1-3]

There may be an increased risk for certain systemic diseases, especially malignant and autoimmune disorders, in individuals with KS.[4,5] KS has also been associated with an increased risk for venous thrombosis and thromboembolism, which was partially explained by hypofibrinolysis due to androgen deficiency.[6] There is very limited knowledge regarding the association between KS and well-known thrombophilic states. To our knowledge, only 4 patients with KS complicated with venous thrombosis were reported to have additional thrombophilic states in the English literature.[7-10] However, no data are present concerning an association between KS complicated with arterial thrombosis and well-known thrombophilic states. We herein present a young man with KS who developed acute arterial thrombosis during testosterone replacement therapy. He was shown to be homozygous for the methylenetetrahydrofolate reductase (MTHFR) gene mutation (A1298C).

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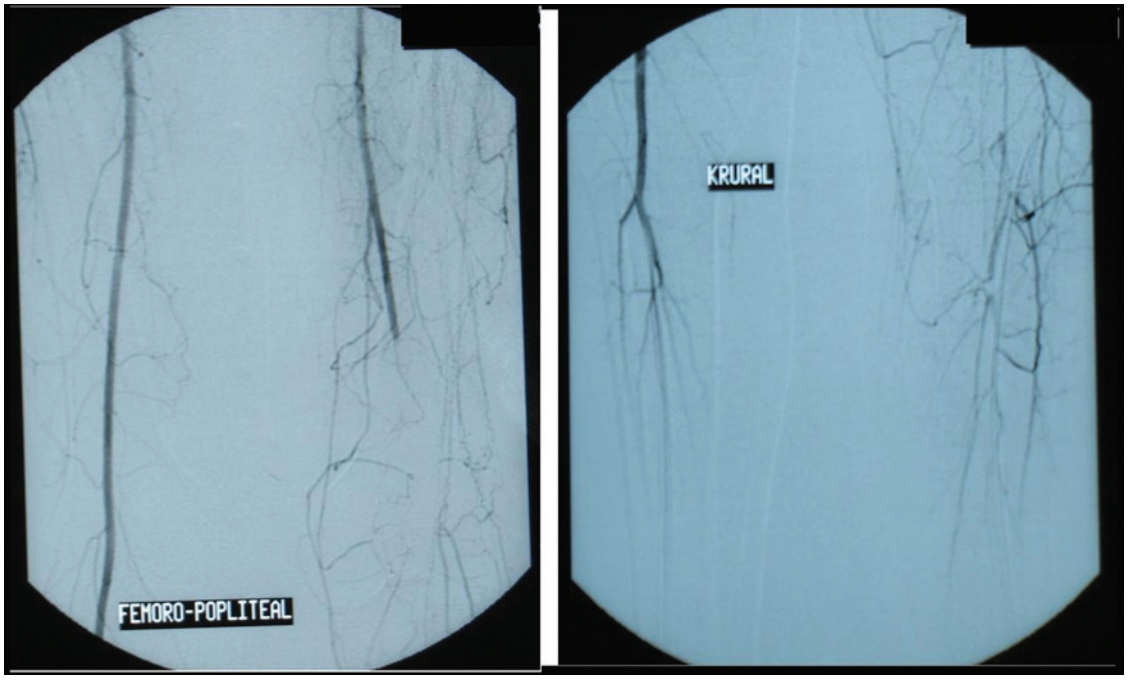

Figure 1. Digital subtraction angiography of the lower extremities demonstrating occlusions of the distal half of the left superficial femoral artery, popliteal artery, anterior tibial artery, and posterior tibial artery.

Case Report

A 30-year-old man had been previously diagnosed as having KS (mosaic form, 46 XY/47,XXY). He had been treated with testosterone replacement without any complication for 6 years until his admission to the emergency department with severe pain in the left lower extremity. Arterial Doppler ultrasonography revealed thrombotic occlusion of the lumen of the left popliteal artery. Digital subtraction angiography of the lower extremities demonstrated that the distal half of the left superficial femoral artery was occluded. Popliteal, anterior tibial, and posterior tibial arteries were also occluded in the left leg, and crural vascularization was supplied by collateral arteries (Figure 1). After cardiovascular surgical intervention, the patient was investigated for hereditary and acquired thrombophilic conditions. The patient's family history was negative for any thrombotic event. He denied the use of any other drug except testosterone. He is a nonsmoker. Complete blood count, serum biochemistry and lipid profile, erythrocyte sedimentation rate, and C-reactive protein levels were within normal limits. Tests for vitamin B12, folic acid, homocysteine, antithrombin III, factor VIII, factor IX, protein S, and protein C were unremarkable. Antinuclear antibody, anticardiolipin antibodies, and lupus anticoagulant were negative. Genotype analyses for factor V Leiden mutation, G20210A mutation of the prothrombin gene, and C677T mutation of the MTHFR gene revealed negative results, although he was homozygous for the A1298C mutation of the MTHFR gene.

Discussion

Hypogonadism in males is associated with an enhancement of fibrinolytic inhibition by means of increased synthesis of the plasminogen activator inhibitor (PAI-1).[11] The reduced baseline fibrinolytic activity may cause increased risk for thromboembolic disease as well as myocardial infarction in hypogonadic males.[11] Likewise, KS patients do have increased risk for venous thrombosis.[6] The increased thrombotic risk in those patients can be partially explained with hypofibrinolysis due to androgen deficiency. Additional genetic or acquired thrombophilic states, including factor V Leiden mutation,[8] antiphospholipid antibody syndrome,[9] G20210A prothrombin mutation plus factor V Leiden mutation,[7] and increased activity of factor VIII coagulant[10] were

detected in KS patients complicated with venous thrombosis in isolated cases.

To our knowledge, arterial thrombotic events have not been reported yet in KS patients. In this study, we presented a young man with KS who developed acute arterial thrombosis during testosterone replacement therapy. Detailed evaluation for the presence of genetic or acquired thrombophilic risk factors revealed that he was homozygous for the A1298C mutation of the MTHFR gene. Association between A1298C mutation of the MTHFR gene and thrombotic tendency is doubtful.[12,13] However, coexistence of this mutation and KS might have generated a hypercoagulable state, which probably would not have been generated by each factor alone.

Enhanced fibrinolytic inhibition in hypogonadic males can be corrected by androgen supplementation.[11] Supplemental androgen may even be a sufficient adjuvant therapy for the treatment of chronic wounds in patients with KS.[14,15] However, in male abusers of anabolic steroids, the net effect on the hemostatic system may paradoxically change from anti- to prothrombotic. It was suggested that an individual threshold dose, above which has thrombogenic effects on platelets and vasomotion, may overcome the profibrinolytic effects on PAI 1.[11] Because our patient developed arterial thrombosis during testosterone replacement, the use of exogenous testosterone, in the presence of KS and homozygosis for the A1298C mutation of the MTHFR gene as additional thrombophilic factors, might have increased his risk of arterial thrombosis.

In summary, we present the first patient with KS who developed an acute arterial thrombotic event during testosterone replacement therapy. Although testosterone replacement is essential in KS patients, and delayed treatment with testosterone may lead to the occurrence of several associated diseases such as osteoporosis or venous thrombosis, it should be kept in mind that arterial thrombotic events may develop during testosterone replacement, especially in patients with additional thrombophilic states.

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