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Pulmonary embolism unmasking concealed Klinefelter syndrome: a case report

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Abstract

Klinefelter syndrome, characterized by the karyotype XXY, is the most common genetic cause of congenital hypogonadism. It commonly presents with underdeveloped testes, gynaecomastia, and infertility. This condition is associated with impaired fibrinolysis secondary to hypogonadism and other concurrent thrombophilic factors, resulting in a hypercoagulable state that predisposes to deep vein thrombosis and thromboembolic events. We report a case of a 21-year-old man who presented with a pulmonary embolism, which subsequently led to the diagnosis of Klinefelter syndrome as the underlying prothrombotic disorder.

Future research facilitating a comprehensive understanding of the pathogenesis of venous thromboembolism in the context of Klinefelter syndrome will lead to improved screening and management strategies.

Key words: Klinefelter syndrome, hypogonadism, pulmonary embolism, venous thrombosis

Introduction

Klinefelter syndrome is the most common congenital cause of primary hypogonadism in males. It is characterized by the presence of one or more additional X chromosomes, which disrupts normal testicular development leading to hypogonadism and infertility.

The diagnosis of Klinefelter syndrome is often delayed until adulthood, as its clinical features typically manifest after puberty. Additionally, it is associated with an increased risk of hypercoagulability, attributed to hormonal imbalances and genetic factors linked to hypogonadism.

In this case report, we describe a previously undiagnosed case of Klinefelter syndrome, revealed following the patient's presentation with pulmonary embolism.

Case presentation

A 21-year-old priest presented with a sudden onset of dizziness, followed by shortness of breath lasting for an hour, accompanied by sweating and palpitations. He denied recent immobilization, leg swelling, history suggestive of connective tissue disorders, thrombosis, or malignancy. There was no significant family history of prothrombotic conditions, and he did not report a history of substance abuse.

Upon arrival at the emergency room, he was tachypnoeic, with a respiratory rate of 36 breaths per minute and a peripheral oxygen saturation of 86%. He was neither pale nor cyanotic. Blood pressure was 80/50 mmHg, with a regular pulse rate of 130 beats per minute. The cardiovascular examination revealed jugular venous distension, a parasternal heave, and a loud pulmonary component of the second heart sound. There were no audible murmurs or radio-radial, or radio-femoral delays. Examinations of the lungs and abdomen were unremarkable. He was conscious, with a Glasgow Coma Scale score of 15/15, and no focal neurological deficits were detected.

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After the resolution of the acute phase, a detailed examination of the patient revealed a height of 193 cm, weight of 106 kg, a Body Mass Index of 28.45 kg/m^2, and an abdominal circumference of 112 cm. He exhibited sparse facial and body hair, with scant axillary and pubic hair (Figure 1). Bilateral, non-tender, and symmetrical gynaecomastia were observed, along with a small penis and bilaterally small, firm testes, consistent with Tanner stage 1. There were no signs of goiter or cushingoid features.

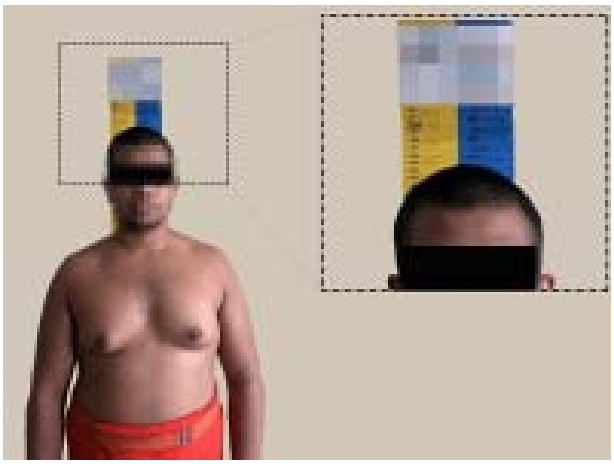

Figure 1. External appearance: tall stature, sparse body hair, and gynaecomastia.

Alongside aggressive resuscitation, an initial bedside diagnostic workup was initiated. Electrocardiogram revealed sinus tachycardia with complete right bundle branch block and right-axis deviation, accompanied by ST-segment depression in leads V3 to V6. High-sensitivity troponin was elevated at 0.096 (normal: 0.015). An urgent chest radiograph showed an enlarged pulmonary conus and oligemic but clear lung fields. A bedside 2D echocardiogram demonstrated a dilated right ventricle and atrium with McConnell's sign: a dilated main pulmonary artery, tricuspid regurgitation, and a "D"-shaped ventricle.

Arterial blood gas analysis showed type I respiratory failure, with a pH of 7.35, PaO_2 of 65 mmHg, $PaCO_2$ of 31.7 mmHg, HCO_3^- of 19.2 mmol/L, and lactate of 1.4 mmol/L. Based on the clinical and imaging findings, there was a strong suspicion of massive pulmonary embolism, prompting an urgent contrast-enhanced computed tomography pulmonary angiogram (CTPA), which confirmed bilateral saddle thrombi extending into the branch arteries (Figure 2).

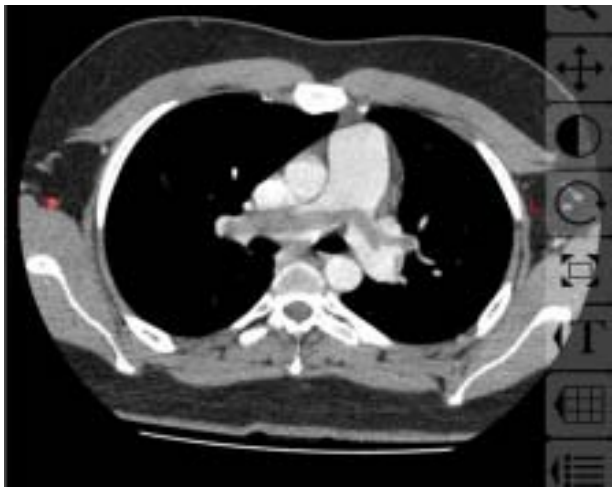

Figure 2. CT pulmonary angiography (axial view) demonstrating a saddle embolus in the main pulmonary arteries.

Laboratory investigations showed a white cell count of 6.47×10^9/L, haemoglobin of 11.7 g/dL, platelet count of 195×10^9/L, INR of 1.2, and APTT of 26 seconds. Subsequent blood tests demonstrated an ESR of 3 mm/hour, C-reactive protein level of 0.4 mg/L, serum creatinine level of 0.9 mg/dL, and HbA1C level of 5.9%.

Biochemical analysis confirmed hypergonadotropic hypogonadism, with a serum FSH of 30.3 IU/L (normal: 1.4-15.4 IU/L), serum LH of 16.23 IU/L (normal: 1.2-7.8 IU/L), serum total testosterone of 3.76 nmol/L (normal: 8.3-28.0 nmol/L), and a serum prolactin level of 218 µg/L (normal: <25 µg/L). Thyroid profile was within normal limits, with a TSH of 3.876 µIU/mL (normal: 0.4-4.0 µIU/mL) and serum-free T4 of 1.26 µg/dL. Dual-energy X-ray Absorptiometry (DEXA) scan revealed a total T-score of -1.9, consistent with osteopenia according to WHO classification and vitamin D (25-hydroxy) level was in the deficient range at 20.28 mg/dL. DEXA scan was indicated to evaluate bone mineral density in the context of hypogonadism and risk of osteoporosis.

Scrotal ultrasound revealed small bilateral testes (left: 15.8×22 mm, 1.8 cm^3; right: 15.5×19.9 mm, 1.5 cm^3) located in the normal position, with normal vascularity and echogenicity. Abdominal ultrasound was negative for organomegaly or para-aortic lymphadenopathy. The sex hormone profile of hypergonadotropic hypogonadism and the clinical findings supported a diagnosis of Klinefelter syndrome, which was confirmed by cytogenetic karyotyping demonstrating 47, XXY (Figure 3).

After three months of thrombosis, thrombophilia screening was conducted and was negative for lupus anticoagulant, beta-2 glycoprotein IgG (1.65), anti-cardiolipin antibody IgG (7.42, <15 GPL), and IgM (8.65, <12.50 MPL). Additionally, three early morning urinary haemosiderin tests were negative.

Given the increased susceptibility of these patients to autoimmune rheumatic disorders (ARD), an anti-nuclear antibody (ANA) test at a specific dilution was performed, yielding a positive result with a titer of 1/100. However, the anti-dsDNA antibody test was negative. Despite these findings, no other clinical, biochemical, or radiological indicators were identified to support the diagnosis of an associated ARD.

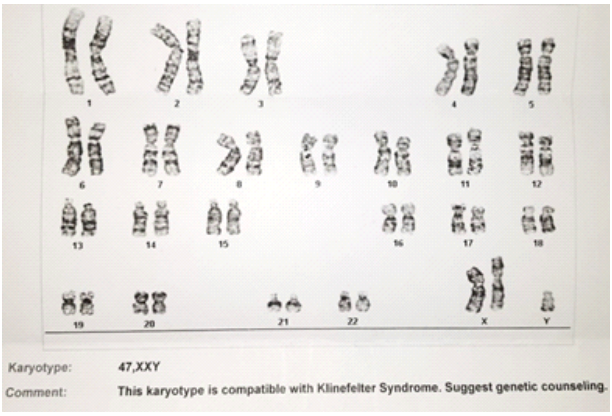

Figure 3. The karyotype shows a 47XXY chromosomal pattern, indicating the presence of an extra X chromosome, which is diagnostic of Klinefelter syndrome.

Therapeutic interventions, follow-up, and outcome

On arrival at the emergency department, the patient received oxygen via face mask, maintaining saturations above 94%. Initial fluid resuscitation had a limited response, and he was subsequently stabilized with a noradrenaline infusion. With a high probability of a massive pulmonary embolism and while awaiting the CTPA, he was anticoagulated with intravenous unfractionated heparin (UFH). After confirmation of a massive pulmonary embolism by CTPA, he was thrombolysed with intravenous alteplase, and UFH infusion continued for five days. Oral anticoagulation with warfarin was initiated after a 72-hour bridging therapy period.

After managing the acute phase, the diagnosis of Klinefelter syndrome was communicated to the patient in a gentle and sensitive manner, with full disclosure of its genetic basis and potential gonadal and extra-gonadal consequences. The importance of lifelong testosterone replacement therapy for maintaining quality of life, cardiovascular health, and bone integrity was emphasized.

At the time, the intramuscular testosterone, which is associated with a dose-dependent risk of erythrocytosis, was the only available testosterone therapy in the country. After careful discussion of the risks and benefits, he was initiated on a low dose of 50 mg intramuscular testosterone, with plans for gradual dose escalation. Close monitoring of haematocrit was planned with a target of maintaining it around 45%. He was also advised regarding possible mood and behavioral changes with the initiation of testosterone therapy. Vitamin D deficiency was treated with oral vitamin D3 supplementation, starting with 50,000 IU weekly for eight weeks, followed by a daily dose of 2,000 IU, with plans to reassess levels in three months.

Discussion

In this case, a young adult male with previously unnoticed clinical features of hypogonadism was unexpectedly diagnosed with Klinefelter syndrome following presentation with a pulmonary embolism. The typical features of Klinefelter syndrome may have been overlooked due to his lifestyle as a priest and the passage through adolescence and early adulthood without medical attention. The diagnosis was revealed when the thromboembolic event was evaluated, highlighting the importance of maintaining a high index of suspicion for Klinefelter syndrome in patients presenting with unexplained venous thromboembolism (VTE), particularly when subtle signs of hypogonadism are present.

Individuals with Klinefelter syndrome have an increased susceptibility to VTE; although the precise underlying pathology remains unclear, it is suggestive of a complex multifactorial aetiology. Over a 20-year comprehensive study, Campbell and Price observed a notable rise in the incidence of deep vein thrombosis (DVT) and pulmonary embolism in a cohort of 412 patients with Klinefelter syndrome.[1] This observation aligns with Winkler's review, which emphasised a credible explanation, supported by two consecutive studies, regarding the influence of androgens on haemostasis.[2] These findings strongly support a clear link between male hypogonadism and decreased fibrinolytic activity, which can be attributed to elevated Plasminogen Activator Inhibitor-1 (PAI-1) levels. It is important to highlight the notable inverse correlation observed between plasma testosterone levels and the synthesis of plasminogen activator inhibitor-1.[2]

Haemostasis involves the formation and dissolution of blood clots, with thrombin and plasmin playing key roles. In this context, PAI-1 is of utmost importance as it restricts the activity of t-PA and fibrinolysis. Notably, our patient exhibited a testosterone level of 3.76 nmol/L (normal range: 8.3-28.0), indicating severe hypogonadism, which could potentially contribute to reduced fibrinolysis and heightened susceptibility to thromboembolism.

The pathogenesis suggests that individuals with Klinefelter syndrome may face an elevated risk of thromboembolism. However, ascribing severe thrombotic events exclusively to hypoandrogenism presents challenges, and it is plausible that one or more inherited thrombophilic factors, like factor V Leiden and prothrombin (factor II) G20210A mutations, could be simultaneously implicated.[4]

The spectrum of associated conditions and complications in Klinefelter syndrome such as metabolic syndrome, diabetes, and systemic lupus erythematosus may also increase the susceptibility to venous thromboembolism.[5,6] As evident in our patient's case, a notably elevated ANA titer indicates the potential development of an ARD.

Conclusion

Individuals with a history of VTE should be evaluated for underlying endocrine abnormalities and chromosomal karyotype analysis when there is a clinical suspicion of Klinefelter syndrome. Future research is essential to better understand the pathogenesis of VTE in the context of Klinefelter syndrome and to guide more effective screening and management strategies.

Author declaration

Consent for publication

The corresponding author obtained informed written consent of the patient to publish the patient's details and accompanying images.

Conflict of interests

None.

Criteria for authorship

The patient's diagnosis, management and manuscript drafting was carried out by CTWM. GGL and DU supervised the patient's management and contributed to the critical revision and refinement of the manuscript. All three authors participated in the conceptual development of the paper and approved the final version of the manuscript.

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