A rare provocation: a case of extensive pulmonary embolism in a man with previously undiagnosed Klinefelter Syndrome

Olivia Carleton, Frances Mein Smith, Cindy Towns

Klinefelter syndrome (KS) is an underdiagnosed aneuploidy characterised by an additional X chromosome and hypergonadotrophic hypogonadism. It has an estimated prevalence of one case in every 660 newborns.1 Most men remain undiagnosed until seeking fertility assistance in later life. The delayed presentation may be due to varied—and at times only mild—physical abnormalities.2 Although the pathophysiology is incompletely understood, recent studies have indicated that KS is also a risk factor for venous thromboembolism (VTE). We present a man who was undiagnosed until presenting with a potentially life-threatening pulmonary embolus. This is the first case in Australasia to report the relationship between KS and VTE.

Case report

A 50-year-old man was referred to hospital by his general practitioner with a 36-hour history of breathlessness and pleuritic chest pain. He took no medications and had no significant medical history. He was previously married but had no children. He had not sought investigation or treatment for infertility. He had no known risk factors for pulmonary embolism (PE). On examination, he was noted to be tall and obese. He was hypotensive (100/80mmHg) with an elevated jugular venous pressure but no oedema; his chest was clear to auscultation. Bilateral gynaecomastia (Figure 1) and sparse facial hair were observed and subsequent exam revealed small volume testicles bilaterally.

Figure 1: Bilateral gynaecomastia in the KS patient (photo used with consent).
He was hypoxic, requiring four litres of oxygen to maintain 92% oxygen saturation. Troponin T and brain natriuretic peptide were raised and his ECG showed anterior and inferior T-wave inversion. Bedside echocardiogram demonstrated septal bowing. Extensive PE was confirmed with computed tomography pulmonary angiogram (Figure 2). He was commenced on dabigatran 150mg BD. Reproductive axis testing revealed low testosterone, raised luteinising hormone and raised follicle stimulating hormone.

Karyotype testing revealed 47 XXY (Figure 3), giving the diagnosis of KS.

Figure 2: CTPA slice showing large PE.

Figure 3: Patient karyotype demonstrating the 47 XXY genotype of KS.
He was reviewed by a haematologist in VTE clinic following discharge and a decision was made for lifelong anticoagulation. A thrombophilia screen was not recommended as it would not change management and the novel anticoagulants were deemed to interfere with the accuracy of testing.

Discussion

This man had no significant risk factors for VTE and hence KS is likely to be the sole provocation in this case. Recent research indicates that this condition should be considered an inherited coagulopathy alongside other more commonly occurring conditions. A prospective cohort study demonstrates that patients with KS have a cumulative incidence of VTE of 8.6% at age 50 and 20.8% at age 70. Similarly, Glueck et al (2017) estimate that the risk of VTE in KS patients is 5–20 times that of their peers.

The mechanism for the increased risk is not entirely clear and may well be multifactorial. Male hypogonadism has been associated with enhanced fibrinolytic inhibition via increased synthesis of plasminogen activator inhibitor (PAI) which may predispose to cardiovascular disease as well as VTE. Vascular abnormalities and platelet hyper-aggregability have been speculated to play a role, and mutations in known thrombophilia genes (Factor V Leiden, Protein C and S and Antithrombin II) have also been reported in KS patients. Other authors postulate that the high rates of VTE associated with KS reflect an interaction of testosterone with underlying thrombophilias.

Testosterone replacement may indeed increase the risk for VTE, however the data quality is low and the association has not been confirmed. Larger trials with VTE as a pre-specified outcome are required before any relationship can be verified. However, our patient was undiagnosed and therefore untreated at initial presentation hence androgen replacement cannot account for the severe presentation. We cannot exclude the role of an additional inherited thrombophilia as he remains untested.

Regardless of aetiology, physicians managing KS patients need to be aware of the increased risks and patients should be monitored very closely, especially if they develop other VTE risk factors. Routine prophylaxis should be applied in high-risk situations such as surgery or immobilisation and consideration may also be given to prophylaxis during long-haul travel. If testosterone replacement is recommended then additional testing for thrombophilia genes should be considered. Similarly, if a KS patient presents with an unprovoked VTE we would recommend thrombophilia testing unless anticoagulation was to be lifelong. Genetic counsellors should also add VTE risk to their education and discussion sessions.

Competing interests:
Nil.

Author information:
Olivia Carleton, Department of General Medicine, Wellington Regional Hospital, Wellington; Frances Mein Smith, Department of General Medicine, Wellington Regional Hospital, Wellington; Cindy Towns, Department of General Medicine, Wellington Regional Hospital, Wellington.

Corresponding author:
Dr Cindy Towns, Department of General Medicine, Wellington Regional Hospital, Wellington.
cindy.towns@ccdhb.org.nz

URL: