Case Report

Klinefelter syndrome in primary care: A case and review

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Abstract

Reviewed here is a case of Klinefelter Syndrome (KS) diagnosed by a primary care physician after recognition of key features of KS, confirmed by karyotype, along with a discussion of factors associated with this patient's diagnosis and care. Recognition of the key features of this syndrome is important in order to provide proper screening, risk mitigation and treatment to these patients.

Keywords: Karyotype, Klinefelter, KS, XXY chromosome

Introduction

Klinefelter Syndrome (KS) is the most common sex chromosome disorder affecting males (estimated at 0.2% of live births). Patients with KS have an XXY chromosomal abnormality that is often the result of non-disjunction during the processes of mitosis or meiosis.[1] KS is often not diagnosed until the third or fourth decade of life, when infertility is generally the trigger for a workup. The delay in diagnosis is most commonly due to lack of recognition of the clinical features and sequelae of Klinefelter Syndrome. A delay in diagnosis of KS can lead to detrimental effects for patients due to lack of awareness of increased risk factors for serious medical conditions.

Case History

A 33-year-old male presented to a primary care physician as a new patient as his girlfriend had suggested he see a physician for what she believed to be small testicles. He personally did not feel anything was unusual regarding his genitalia, as he was able to have erections and achieve orgasm with ejaculation. His past medical history included major depressive disorder, generalized anxiety disorder (both treated with an SSRI), testosterone deficiency/hypogonadism (treated with testosterone cypionate injections), learning disabilities throughout his schooling, and two deep vein thromboses (treated with lifelong warfarin). He reported no surgical history and no known drug allergies. Family history was unremarkable for genetic abnormalities in parents and siblings. His social history revealed a high school education level, current full-time employment (stocking merchandise in a warehouse), and no current or former use of tobacco, alcohol, or other drugs. He exercised daily with weightlifting and had been using protein supplements due to being self-conscious about his body image. In his review of systems, the patient denied any recent illnesses, fevers, penile discharge, difficulty with mood, or history of sexually transmitted infections. He voiced no other concerns regarding his presentation.

Pertinent laboratory review revealed a serum testosterone level of 100 ng/dL (reference range: 300–1000 ng/dL) one year prior to his presentation to the office at his prior primary care office. He received injections every two weeks and his subsequent serum testosterone level improved to 450 ng/dL.

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On physical examination, the patient was 78 inches (6 feet, 6 inches) tall and weighed 205 pounds with a body mass index (BMI) of 23.7. His other vital signs were stable. He was awake, alert, oriented, and in no acute distress. His head was normocephalic and atraumatic. He did not have any facial abnormalities. Heart rate was regular without any murmurs, rubs, or gallops. His chest did show features of mild gynecomastia. Lungs were clear bilaterally without rales, wheezing, rhonchi, or accessory muscle use. Abdomen was soft, non-tender, and non-distended with bowel sounds heard in all quadrants. Genitourinary exam showed an uncircumcised penis with testicles 2.5 cm by 2.5 cm symmetrically round, firm to palpation, and descended into the scrotum bilaterally. Cranial nerve examination was unremarkable. Mood and affect were appropriate but he did show difficulty comprehending the discussion of his visit evidenced by repeating questions and answers as reassurance of understanding the conversation. Based on the history and physical exam findings, this patient was referred for a karyotype genetic analysis. The karyotype [Figure 1] confirmed the diagnosis of Klinefelter syndrome by the presence of the XXY genotype.

Discussion

Klinefelter syndrome affects approximately 1 in 650 newborn boys (less than 0.2%), and approximately 64% of cases are undiagnosed.[1] It is not inherited but rather occurs due to nondisjunction or mosaicism during anaphase of mitosis, meiosis I or meiosis II.[2] The addition of an extra X chromosome, which is the key genetic feature of Klinefelter Syndrome, occurs during gametogenesis in one of the parents. Nondisjunction prevents

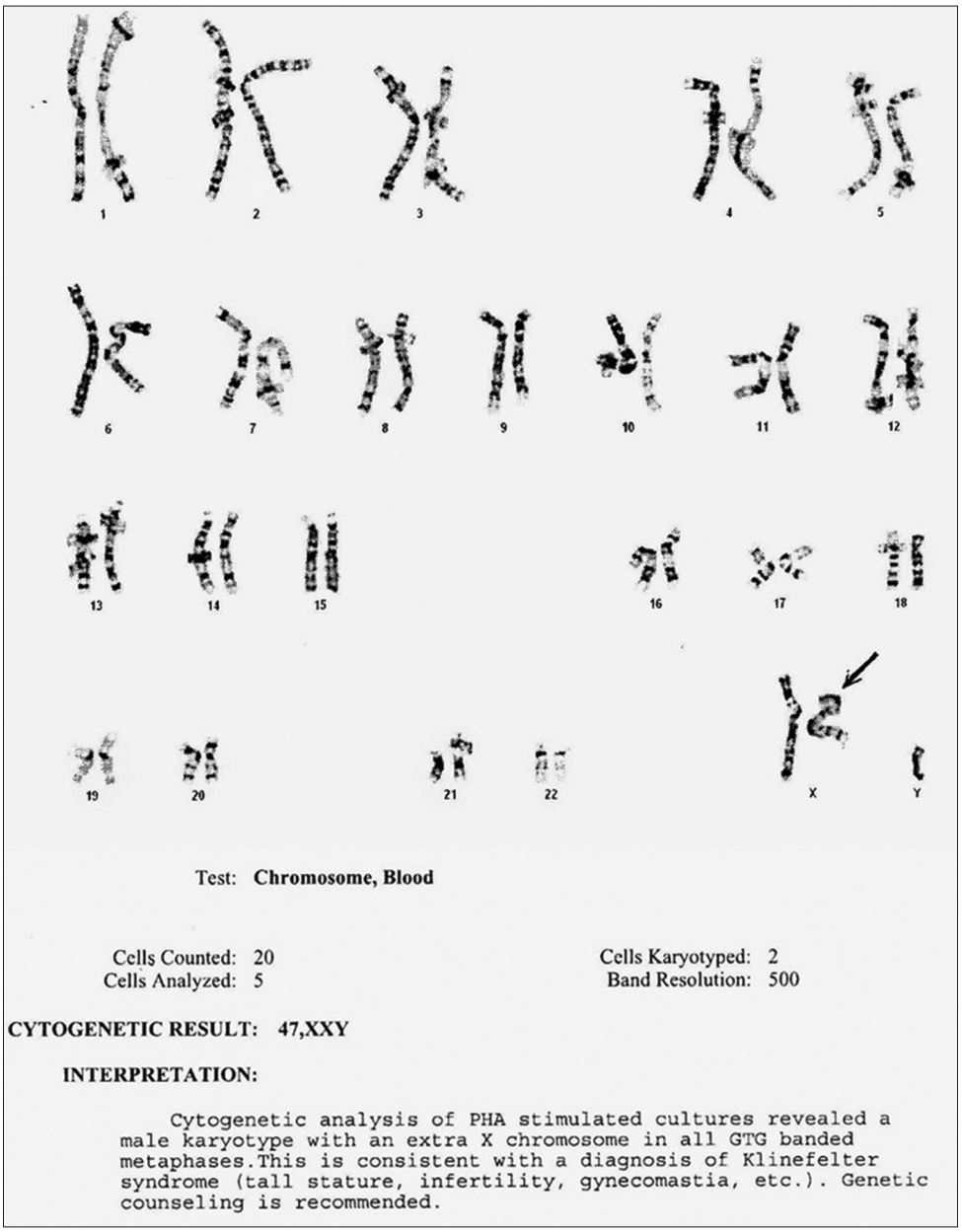

Figure 1: Karyotype and Interpretation (*arrow indicates extra X chromosome*)

X chromosomes from being distributed normally among reproductive cells as they form leading to an egg or a sperm cell with an extra copy of the X chromosome. Klinefelter syndrome occurs if an egg with an extra chromosome (XX) is fertilized by a sperm cell with one Y chromosome or if a sperm containing an X chromosome and Y chromosome (XY) fertilize an egg with a single X chromosome. The XXY genotype results in Klinefelter syndrome. Another variant called Mosaic Klinefelter syndrome (46, XY/47, XXY) occurs as a random error during cell division early in fetal development. Genetic mosaicism occurs when an individual possesses two or more genetically different sets of cells.

Infertility due to azoospermia is one of the most common presenting symptoms of KS, therefore, it is often not identified until the third or fourth decade of life as a result of semen analysis as part of an infertility workup.[1,2] The lack of testosterone production resulting from hypogonadism may lead to delayed or incomplete puberty, gynecomastia, decreased muscle mass and bone density (leading to hypotonia and osteoporosis, respectively), a reduced amount of body hair and other distinguishing male secondary sex characteristics. Genitourinary abnormalities such as cryptorchidism, hypospadias, and micropenis have also been reported.[3] Individuals with Klinefelter syndrome are often noted to be taller than their peers. Other features associated with Klinefelter patients include radioulnar synostosis (abnormal fusion), fifth finger clinodactyly, and pes planus. Learning disabilities in speech, language, and reading may be apparent. Anxiety and depression symptoms commonly manifest as well.[2]

Individuals with Klinefelter syndrome show an increased predisposition (45%–50% incidence) to type 2 diabetes mellitus, hypertension, hyperlipidemia, and obesity (collectively, metabolic syndrome) in addition to aortic valve dysfunction, clotting disorders precipitating deep venous thrombosis and pulmonary embolism, and peripheral vascular disease. Cerebrovascular disease risk is higher with an increase in the incidence of subarachnoid hemorrhage, saccular aneurysm, and thromboembolic cerebrovascular accidents. Those with gynecomastia are at a higher risk of developing breast cancer and require appropriate screening including self-examinations and possibly mammography.[1-4]

Diagnosis of Klinefelter syndrome is challenging, as KS occurs as a spectrum of genotypical and phenotypical abnormalities. Physical traits (phenotypic characteristics) become more apparent later in life if present at all, resulting from decreased testosterone production secondary to hypogonadism.[1,4] Severity of phenotypic dysmorphia is believed to be proportional to the severity of aneuploidy and genital dysfunction. A majority of patients remain undiagnosed with an increased risk and predisposition to cardiovascular, cerebrovascular, and metabolic co-morbidities as well as male breast cancers.[2,3,5] Early intervention is effective at mitigating and managing co-morbid conditions as well as mortality risk factors.[1,2] The variation in clinical manifestations poses a diagnostic challenge to physicians as do the social determinants of health needing to be addressed in concordance.[3-5]

Several clues were present in the initial evaluation of this patient that were suspicious for underlying KS, including the history of low testosterone, deep vein thrombosis and mood disorders, along with his learning difficulties during schooling years. He had some of the more common phenotypic features as well, including tall stature and gynecomastia. Diagnosis of Klinefelter Syndrome ties many of his physical and mental health conditions together and will help lower his risk for further complications later in life through effective screening and risk factor mitigation. It is important for primary care providers to recognize key features of Klinefelter Syndrome, as it is rare, but common enough that a primary care provider may encounter patients with this syndrome who may need additional targeted screening and treatment.

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Conflicts of interest

There are no conflicts of interest.

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