CLINICAL VIGNETTE

46,XX Male Syndrome: A Rare Cause of Male Infertility

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Case

A 25-year-old man presented to discuss starting testosterone therapy for hypogonadism. He was born with male genitalia and started puberty at a similar time to his peers in junior high school. He had normal penile development, voice changes, and growth. However, he noticed his testicles were not growing and at the time, his parents told him his karyotype was 46, XX based on his mother's *in utero* testing.

The patient reported low energy, chronic fatigue, and mildly depressed mood. He also had decreased libido. He denied erectile dysfunction. He had spontaneous morning erections up to 5 times per week. He shaved his face once every 3 days. He had hair on his extremities but no hair on his chest or back. He was shorter than his immediate male family members. He recalled a previous morning testosterone level of 258 ng/dL (low to low normal). He had azoospermia on a prior semen analysis.

The patient had no other past medical or surgical history. He had never smoked and drank alcohol occasionally. He had a university degree. His family history included healthy parents (father 173 cm, mother 165 cm), an older brother (178 cm), and an older sister (163 cm).

On examination, the patient was 167 cm and 53 kg with body mass index 18.9 kg/m^2. He appeared healthy. He was normocephalic, with normal spacing between his eyes, normal ear size, and facial hair. He did not have hair on his chest nor over his abdomen. He had a normal-appearing penis. He had bilateral small, soft, descended testes. He has normal muscle bulk, strength, and tone and reflexes. He had normal arm length, palm size, and finger length.

Fasting morning laboratory studies showed normal complete blood count, comprehensive metabolic panel, thyroid function, and estradiol levels. His testosterone was low normal, including total 318 ng/dL (300-1080), free 57.1 pg/mL (47-244), and bioavailable 179.7 ng/dL (130-680) levels. Follicle-stimulating hormone (FSH) was high at 30.2 mIU/mL (1.6-9), as was luteinizing hormone (LH) at 31.4 mIU/mL (2-12). Sex hormone binding globulin levels were normal.

Karyotype and fluorescence in situ hybridization analysis were performed. Chromosomal analysis showed 46,X,add(X)(p22.3).ish der(X)t(X;Y)(p22.3;p11.3)(SRY+), which is a 46,XX karyotype.

The patient began testosterone gel therapy with one pump applied daily to his bilateral shoulders. His energy, libido, and mood improved somewhat after starting testosterone. Repeat testosterone testing revealed slightly low total 258 ng/dL (300-1080), free 44.2 pg/mL (47-244), and bioavailable 139 ng/dL (130-680) levels and testosterone gel dose was increased to two pumps applied daily. Subsequent laboratory testing showed testosterone levels in the normal range: 650 ng/dL, 132 pg/mL, and 423.4 ng/dL for total, free, and bioavailable, respectively.

Discussion

Hypogonadism can be caused by primary (at the level of the gonads) or secondary (at the level of the hypothalamus gland or pituitary gland) dysfunction. While often idiopathic, primary hypogonadism can also be due to prior infection, trauma, drug use, or congenital disorders.

A rare cause of primary hypogonadism is 46,XX male syndrome, which affects 1 in 20,000 males,[1] including our patient. The syndrome, first documented in 1964, was previously known as de la Chapelle syndrome[2] and may also be referred to as 46,XX testicular disorder of sex development.[3] Individuals with 46,XX male syndrome have a male phenotype but a 46,XX genotype.

In 80-90% of cases, the cause is due to unequal translocation of the sex-determining region Y (SRY) gene, which encodes the testis-determining factor driving male fetal sex development, from the short arm of the Y chromosome onto to the short arm of the X chromosome (or a non-sex chromosome) during meiosis of the individual's father.[4-6] This process is almost always sporadic.[1,7] In the other 10-20% cases of 46,XX male syndrome, individuals are SRY-negative and there is no translocation. The male phenotype may be due to hidden mosaicism of the SRY gene or due to mutations of other genitalia-determining genes, such as the SOX9 gene located on chromosome 17,[8,9] or genes on the X chromosome.[6] These SRY-negative individuals may have more genital ambiguity and may be diagnosed earlier in life.[7,10]

Typical phenotypic characteristics of individuals with 46,XX male syndrome include small, soft testes, normal penis, azoospermia, and sometimes shorter stature, gynecomastia from increased aromatization of testosterone in peripheral tissues, reduced hair growth, cryptorchidism, or hypospadias.[6,11] The

mean height of 46,XX male syndrome individuals was 166 centimeter in one review[11]; this shorter stature is attributed to the absence of pubertal growth from testosterone or other Y-chromosome specific genes/growth factors.[12] Due to azoospermia and an inability to conceive, individuals may be diagnosed during evaluation of infertility. The syndrome is responsible for 2% of male infertility cases.[1] As in our patient, individuals with 46,XX male syndrome may have normal for age testosterone levels during puberty but evidence of hypergonadotropic hypogonadism (low testosterone levels with elevated FSH and LH levels) later in life.[13]

Evaluation and management of individuals with 46,XX male syndrome can include genetic counseling, testosterone replacement therapy, bone density testing to screen for osteopenia or osteoporosis (due to hypogonadism), pelvic imaging to look for Mullerian duct remnants and/or cryptorchidism, and surgery to address gynecomastia, cryptorchidism, or hypospadias.[11] Due to the absence of protective genes located on the Y chromosome, it has been hypothesized that this may confer higher risk of systemic lupus erythematosus (SLE) and scleroderma; however, there is a stronger reported association between SLE and Klinefelter syndrome (47,XXY), another cause of male hypogonadism and infertility.[14]

We report a case of 46,XX male syndrome, in which karyotype analysis confirmed 46,XX with the presence of the SRY gene. 46,XX syndrome is an uncommon cause of hypogonadism and infertility. It is important to make this diagnosis so that it can be treated and in the case of trying to conceive, other options for biological fertility can be discussed.

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