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CASE REPORT

45,X/46,XY Mosaicism in an 18-year-old Girl with Primary Amenorrhea: A Case Report*

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Abstract

45,X/46,XY mosaicism is a rare disorder with a wide heterogeneity in its manifestations. An 18-year-old girl was referred to the endocrine clinic for investigation of her primary amenorrhea. Clinical examination was unremarkable. Hormonal profile was consistent with primary ovarian insufficiency and human chorionic gonadotropin (hCG) stimulation did not show evidence of active testicular tissue. Karyotyping studies by G-banding revealed a 45,X/46,XY karyotype. She was diagnosed with mosaic Turner syndrome with Y chromosomal material and investigation was performed to identify the presence of male gonads due to the risk of gonadal malignancy. Magnetic resonance imaging (MRI) of the pelvis did not show evidence of gonads. Laparoscopic exploration was proposed but the patient and parents refused opting for conservative management. This case highlights the challenges in the management of this rare condition.

Key words: Mixed gonadal dysgenesis, Turner syndrome, Y chromosome, sex chromosome aberrations, 45,X/46,XY mosaicism

INTRODUCTION

Disorders of sexual development (DSD) consist of congenital conditions in which development of the chromosomal, gonadal or anatomic sex is atypical.[1] Gonadal dysgenesis is part of the subset of DSD and is characterized by incomplete or defective gonadal development as a result of either structural or numerical anomalies in the sex chromosomes or mutations in the genes involved.[2] This is further divided into complete (Swyer syndrome) and partial gonadal dysgenesis depending on the morphology of the gonads. In partial gonadal dysgenesis, the percentage of cells with intact XY genotype determines the degree of testicular differentiation.[3] Deficiency of Müllerian inhibiting substance and testosterone results in incomplete internal and external genital masculinization.[3] An X-linked molecule, DAX1 (duplicated in adrenal hypoplasia congenita on the X chromosome) has also been proposed to play a role in suppressing testicular differentiation.[3] A common karyotype is 45,X/46,XY although 46,XY or other forms of mosaicism can be seen.[2] 45,X/46,XY mosaicism is rare with estimated detection rates of 1.7 per 10,000 newborns and most reports are from case series.[4] In Turner syndrome, Y chromosome material has been reported between 5 to 12 percent of patients.[5,6] Individuals may present with a wide spectrum of manifestations ranging from phenotypic females with or without virilization, ambiguous genitalia or Turner features to phenotypic males and are typically short or of normal height although the reason for this is unclear.[7] This condition may go unrecognized into adulthood unless there are gross features of Turner syndrome, growth retardation, pubertal delay or sexual ambiguity. Adult males may present during investigation for infertility. Traditionally, gonadectomy has been recommended in all individuals with presence of Y chromosome material.[8] In complete gonadal dysgenesis, there is a high risk of gonadal malignancy. Bilateral gonadectomy is recommended as soon as the diagnosis is established.[2] In contrast, the evidence is inconsistent for partial gonadal dysgenesis. In light of more recent studies, there has been a move towards a more individualized and conservative approach to decision-making in these individuals, taking into account their phenotype and certain risk factors.[2,9] There is also lack of evidence regarding the utility of imaging and tumour markers as part of surveillance in those who decide for conservative management.

CASE

An 18-year-old girl of Chinese descent was referred to the adult endocrine clinic for further investigation of her primary amenorrhea. She had an uneventful antenatal history and was born with normal female external genitalia. She is an only child and there was no history of consanguinity. There were no major childhood illnesses or admissions to hospital. According to her parents, her developmental milestones were normal and academic performance was average. Among her peers in class, she was on the shorter side but otherwise did not have any issues with her social interactions and was a reasonably well adapted child. Academic performance was average. She had an aunt on her mother's side who had delayed menarche, hence the delay in seeking medical treatment.

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A year prior, she had visited a gynaecologist and had been given a trial of oral contraceptive pills leading to commencement of her menstrual periods which stopped upon cessation of the pills. She is not sexually active and denies use of any other medications or substances.

She is 145 cm tall with a mid-parental height of 152 cm. Her weight is 48 kg with a body mass index of 22.8. She has no acne, hirsutism or deepening of voice. There were no dysmorphic or obvious Turner features. External genitalia appeared female. Breast development was Tanner 3 and pubic hair was Tanner 2. There was no clitoromegaly or palpable gonads. Cardiovascular examination was normal.

Blood investigations reveal hypergonadotropic hypogonadism with normal prolactin, thyroid function test and insulin like growth factor-1 (IGF-1) (Table 1). HCG stimulation test was performed showing no increase in serum testosterone post-stimulation (Table 1) suggesting that there is no active testicular tissue. These were taken after the hormonal pills were stopped. Bone age was 14 years of age. Magnetic resonance imaging (MRI) of the pelvis was done which showed a small and atrophic uterus (Figure 1). No structures resembling ovaries or testicular tissue were identified. An echocardiogram was performed to screen for cardiac malformations showing a normal aortic valve and aortic root. Standard chromosomal analysis by G-banding on peripheral blood revealed 2 different cell types, one with single X chromosome (4 spreads) and one with XY chromosome (60 spreads). Careful discussion was carried out with the patient and her parents disclosing her diagnosis, gonadal status, consequences on fertility and the possibility of gonadal malignancy in view of the presence of Y chromosome material. The patient is comfortable with her gender identity as a female and did not express any gender dysphoria. Fertility was not an active concern at the time as she was still single, however it was explained that she would be unable to conceive normally. Laparoscopic exploration was recommended for assessment of any atypical gonads followed by gonadectomy. However, the patient and her family were not keen for an invasive procedure and opted for conservative management for the time being. She was started on hormonal replacement therapy for prevention of the long-term consequences associated with primary ovarian insufficiency and is under regular follow-up and monitoring for medical and endocrine complications related to Turner syndrome. Option for interval imaging for surveillance for gonadal malignancy was also discussed with the family.

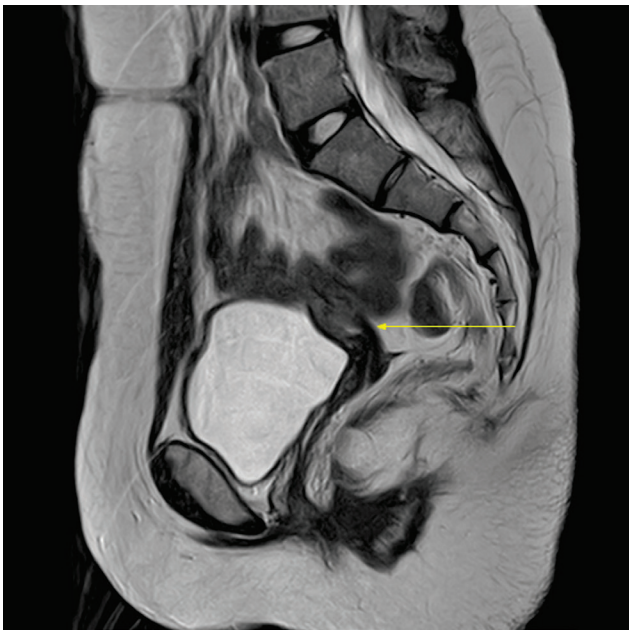

Figure 1. MRI pelvis. Image shows small and atrophic uterus (yellow arrow).

Table 1. Hormonal profile

Serum oestradiol	<70.0 pmol/L (follicular phase 70.0-670.0)
Serum follicle-stimulating hormone	101.7 IU/L (follicular phase 3.5-16.0)
Serum luteinizing hormone	36.4 IU/L (follicular phase <15.0)
Serum Insulin-like growth factor-1	245.0 ng/ml (14.0 - 483.0)
Serum testosterone (baseline)	0.52 nmol/L (0.30 - 2.00)*
Serum testosterone (post hCG)	0.59 nmol/L (0.30 - 2.00)*
Serum Prolactin	411.4 mIU/L (108.78 - 557.13)
Free T4	13.0 pmol/L (9.0-19.1)
Thyroid stimulating hormone (TSH)	1.63 mIU/L (0.35 - 4.94)

* Normal laboratory reference ranges for testosterone in females. No specific cutoffs available for hCG stimulation.

DISCUSSION

In partial gonadal dysgenesis, there is wide heterogeneity in phenotype ranging from males with varying degrees of masculinization of the external genitalia to females with or without features of Turner syndrome. Imaging findings can range from absent to fully developed Müllerian structures, depending on the degree of testicular dysgenesis.[2] Prior studies have shown that the proportion of the cell lines in the blood karyotype does not appear to accurately reflect the phenotype.[7] However, there is evidence to suggest that the mosaicism ratio in various tissues may explain the variability in the phenotypes.[10] The ratio exhibited in different tissues can vary widely, hence tissues with a higher ratio of 45,X/46, XY fragments may be more likely to exhibit Turner syndrome phenotype.

In our patient, we were unable to perform the analysis on the gonads, however a higher mosaicism ratio and consequent lack of Y chromosome in the gonadal tissues could explain her predominantly Turner phenotype. A study evaluating 16 Chinese patients with 45,X/46,XY mosaicism demonstrated that most of the female patients had persistent Müllerian structures with streak or unidentified gonads which present as an infantile or rudimentary uterus with 2 patients having a normal-sized uterus.[7] These findings are consistent with those of our patient. In one case series, absence of gonadal tissue was noted in 18% of patients with 45,X/46,XY mosaicism who underwent gonadectomy.[11] It is hypothesized that the gonadal anlage, when unable to develop to mature stage, regressed by apoptosis.[11] Similar to our patient, patients with partial gonadal dysgenesis usually demonstrate hypergonadotropic hypogonadism with decreased levels of serum testosterone and minimal or no elevation in testosterone response to hCG stimulation as well as reduced anti-Müllerian hormone levels.[7]

In the past, prophylactic gonadectomy has been routinely recommended, although it has been debated whether this may constitute over-treatment. Presence of Y chromosome material increases the risk of gonadal malignancy with gonadoblastoma being the most common germ cell

tumour seen in individuals with XY gonadal dysgenesis.[12] For individuals with 45,X/46,XY (with or without Turner stigmata) and its variants, the estimated tumour prevalence is between 15 to 40%.[13] Notably, the rate was lower in Turner syndrome girls with Y chromosome material, estimated to be between 7% to 10% in one study.[14] Furthermore, no cases of gonadoblastoma or dysgerminoma were identified in a study of the Danish Cancer Registry.[15] Possible explanations include the lack of regulatory Y chromosome genes on the X chromosome affecting the level of potential oncogenes like the H-Y transplantation antigen and other potential carcinogenic oncogenes resulting in a lower incidence of gonadoblastoma in Turner syndrome females with Y chromosome material compared to XY females.[13] Studies have suggested that the degree of virilization of the external genitalia may reflect gonadal differentiation and thus the risk of tumour in 45,X/46,XY mosaicism.[2,11] The risk of developing a tumour was noted to be highest in individuals with ambiguous phenotype, 52% compared to 2.2% in females without signs of virilization.[11] Other proposed risk factors for development of malignancy include intra-abdominal location of gonads and the presence of various immunohistochemical markers on gonadal tissue in particular expression of OCT 3/4 (octamer binding transcription factor 3/4) and TSPY (testis-specific protein-Y).[16] Plescakova et al., proposed a malignancy risk stratification criteria by placing OCT3/4 positive gonads at intermediate to high risk, TSPY expression at high risk and normal gonads or negative OCT3/4 as low risk categories.[9] Our patient has no evidence of virilization with no identifiable gonads on imaging. Taking this into consideration, it could be argued that she may be at a low or intermediate risk category and a "watch and wait" strategy may be plausible.

Imaging is generally used to evaluate presence and type of Müllerian structures, localize gonads and detect any malignant features.[16] However, small tumours or dysgenetic gonads may be missed due to the heterogeneity of their size and appearance.[16] Although limited, studies have shown that there is poor correlation between preoperative imaging and gonadal pathology. Pelvic ultrasound is the most easily accessible, non-invasive and quick imaging study to perform, although it may be highly dependent on transducer resolution and operator experience. Ultrasound rates for identifying intra-abdominal gonads in individuals with DSD range from 47 to 54%.[16,17] An MRI may have better sensitivity compared to ultrasound scan being able to identify gonads in 29% to 57% of DSD individuals.[2,18] However MRI scans were not good at identifying pre-malignant changes.[18] Hence, the only definitive way to identify a gonadal tumour is gonadectomy. In view of the limited accuracy and potential differences in imaging equipment and technique between smaller centers and tertiary referral centers with paediatric trained radiologists, imaging surveillance for patients who wish to defer gonadectomy remains a challenging aspect of care. In our patient, imaging failed to reveal presence of gonadal tissue. This may be consistent with other studies showing absence of gonads in some patients, but we were unable to completely rule out small tumours, dysgenetic or streak gonads. Whilst tumour markers have been used for diagnosis and follow-up of some germ cell tumours, use of markers such as alpha fetoprotein, lactate dehydrogenase and beta-human chorionic gonadotropin for early detection of gonadal tumours in patients with XY partial gonadal dysgenesis has not been well established. However, positive tumour markers in the setting of a gonadal mass with or without discordant pubertal characteristics would warrant a staged surgical procedure which would involve a laparotomy rather than laparoscopy.[19]

A careful review of the physical features, hormonal evaluation, karyotype, imaging and assessment of malignancy risk should be undertaken and the findings discussed between the health care provider with the patient and family. Ethical dilemmas regarding future gender identity and hormonal and fertility preservation have to be balanced with the risk and benefit of surgery, bearing in mind the challenges faced for future surveillance in those who decide to defer gonadectomy. Our patient is phenotypically female and has been reared as a female for her whole life and is thus comfortable with her gender identity. However, earlier gender assignment or reassignment may be a significant issue and may require detailed psychosocial assessment. Follow-up for the patient should also encompass monitoring of physical health including possible Turner complications, hormone replacement and addressing future fertility concerns. In Asian cultures, female infertility may preclude future marriage prospects and carry a stigma. Where available, involvement of an experienced multidisciplinary team is key to ensure the best management for the patient and family.

CONCLUSION

We present a rare disorder of 45,X/46,XY with heterogenous manifestations. Work-up revealed a diagnosis of mosaic Turner syndrome with Y chromosomal material. This case highlights management challenges of a rare endocrine condition.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

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