45,X/46,XY mosaicism presenting with isolated unilateral cryptorchidism and a normal blood karyotype

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Abbreviations: MPH: mid parental height; GH: growth hormone; SDS: standard deviation score; IGF-1: Insulin-like growth factor 1

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Abstract

Context: 45,X/46,XY mosaicism is a disorder of sex development leading to abnormal gonadal development and to unpredictable genital phenotype, growth and pubertal development.

Case Description: A two year old male presented with a right impalpable testis. Blood karyotype was 46,XY. A laparoscopy performed for right orchidopexy revealed a right streak gonad with Mullerian structures, while on the left side a normal descended testis was present. The karyotype of the removed gonad was 45,X/46,XY. The child grew along the 2nd centile, within the mid parental height (MPH) range, until the time of puberty, when linear growth worsened due to a lack of a pubertal growth spurt and growth hormone (GH) therapy was initiated. He developed spontaneous puberty (13 years of age) and he showed normal pubertal progression. However, from the age of 15 years, he had low normal testosterone, raised FSH and reduction of Anti-mullerian hormone and Inhibin B, possibly suggestive of declining testicular function. His final height was -2.24 SDS (-2.4 SDS at GH start; MPH -1.6 SDS).

Conclusions: Our case describes a mild male phenotype associated with 45,X/46,XY mosaicism characterized by unilateral cryptorchidism, spontaneous onset of puberty and normal blood karyotype. The case illustrates the difficulties inherent in making a diagnosis of 45,X/46,XY mosaicism when there is no genital ambiguity, and makes the point that growth and testicular impairment may occur, mostly manifesting during adolescence. An early diagnosis is crucial to initiate careful monitoring for growth and pubertal disorders, increased tumor risk and fertility issues commonly seen in these children.

Précis

Our case illustrates a very mild male 45,X/46,XY phenotype without ambiguous genitalia, with normal blood karyotype and with mosaicism detected only on the gonadal tissue.

INTRODUCTION

45,X/46,XY mosaicism is a rare (1.7/10000) sex chromosome disorder of sex development. Heterogeneous phenotypes have been associated with 45X/46XY mosaicism encompassing females with and without Turner syndrome stigmata and males with varying degrees of masculinisation of external genitalia [1]. The conventional karyotype studied in the peripheral lymphocytes has several limitations [2-3] and does not predict the chromosome constitution of other body tissues [4]. Indeed, in some cases, mosaicism can be detected in the gonadal tissue only.

We describe the case of a boy presenting with a very mild genital phenotype, a normal peripheral karyotype, and diagnosed with 45X/46XY mosaicism on the gonadal karyotype only.

CASE REPORT

A two year old child, raised as a male, presented with an impalpable testis on the right side. He had normal phallic and scrotal development with a normally descended left gonad. The conventional blood karyotype was 46,XY in 30 cells examined. Right orchidopexy was attempted but, instead of a testis, a streak gonad with a fallopian tube was visualized on the right side. Subsequent examination under anaesthesia, with cystoscopy and laparoscopy, revealed a normal left palpable testis in the scrotum and a right streak gonad with surrounding tubular structures, possibly Mullerian remnants. The prostatic urethra and bladder were normal. The histology of the removed right gonad and surrounding structures demonstrated a fallopian tube, a small streak gonad with no identifiable seminiferous tubular or follicular structures, a uterus with normal

immature endometrium and myometrium, and some scattered male ductal structures. The gonadal karyotype revealed mosaicism with 45 X in 27 cells and 46 XY in 13 cells analysed.

Given the diagnosis of 45,X/46,XY mosaicism, the child started regular surveillance for growth and pubertal development, tumor risk, infertility and complications of Turner syndrome. No associated autoimmune, cardiac and urinary tract phenotypes were detected at diagnosis and during the follow-up. The patient's growth pattern and pubertal progression are shown in *Figure 1*. Up to the age of 8 years, he demonstrated a normal growth velocity along the 2nd centile (-2 SDS), appropriate for his mid-parental height (-1.6 SDS), and a joint decision was made with the family to wait before starting Growth Hormone (GH) treatment. At 10.25 years, he showed a deceleration in his growth velocity (4.1 cm/year, -1.2 SDS) with an advanced bone age of 11.5 years, giving a predicted adult height of 156 cm (<-2 SDS). GH therapy was initiated (0.03 mg/kg/day and subsequently titrated by IGF-1 concentrations), with significant improvement of the growth rate after one year of treatment (8.2 cm/year, +3.3 SDS). At the age of 13.15 years, he spontaneously entered puberty. During the follow-up period, he progressed normally through puberty, but he showed a poor pubertal growth spurt. At the last follow-up (15.98 years), his near-final height was 155.4 cm (-2.24 SDS) and his pubertal staging was genitalia 4-5, pubic hair 4, axillary hair 1, with a left testis volume of 15-20 ml. At the last biochemical assessment, testosterone was at the lower end of the normal adult range, and FSH was slightly elevated (*Table 1*). Anti-mullerian hormone and Inhibin B performed on two occasions (13 and 15 years of age) were normal, but showed a significant decrease over time (*Table 1*).

DISCUSSION

45,X/46,XY mosaicism is a rare genetic finding, leading to complex management issues with respect to gender of rearing and to unpredictability of the genital and gonadal phenotype of the affected children [1,5]. The relative distribution of the 45,X and 46,XY chromosomal cell lines among different tissues probably accounts for this wide phenotypic variation. The blood karyotype has several limitations: the number of cells examined can change the karyotype results and the percentage of the 45,X cell line can also decrease over time [3,5].

Three cases have been reported so far of discordance between blood (46,XY) and gonadal (45,X/46,XY) karyotype [2,6,8]. Two patients presented with ambiguous genitalia at the age of 1 year [2] and with a left undescended testis and penoscrotal hypospadias at the age of 16 years [6], respectively. The third case was a neonate with ambiguous genitalia in whom chromosome Y-derived sequences were detected in the dysgenetic gonad and skin fibroblasts [8]. To our knowledge, our patient is the phenotypically mildest reported case of 45,X/46,XY mosaicism (isolated unilateral impalpable testis with normal male genitalia and spontaneous puberty) diagnosed only on the gonadal karyotype. Nonetheless, in keeping with previously reported cases [7], from the age of 15 years, our patient showed biochemical features of possible declining testicular function. It is well-known that the majority of 45,X/46,XY patients born with ambiguous genitalia are infertile. However, even in patients with mild phenotypes in childhood, spermatogenesis may be impaired in adulthood [7]. Therefore, at diagnosis, possibilities of fertility preservation should be discussed with the patient and his family [1].

45,X/46,XY patients exhibit an increased tumor risk, not only when abdominal undifferentiated gonads are present, but also in dysgenetic or "apparently normal" intrascrotal testes [9,1,7]. In dysgenetic gonads, the formation of in situ gonadoblastoma or of an invasive germ cell tumor occurs in 15- 52% of cases [9]. However, the risk of germ cell malignancies is mainly defined by histological markers that do not distinguish "maturation-delayed" from "malignant" germ cells, probably leading to an over-diagnosis of cancer and also to over-treatment by gonadectomy [9, 10]. Although in the past gonadectomy was recommended, a more conservative approach is now preferred to allow endogenous hormone production and therefore spontaneous puberty, and to delay irreversible surgery until adulthood. Individualized management has recently been suggested in 45,X/46,XY patients taking into consideration genetic factors, the localization of the gonad, the age and cooperation of the patient, and the histological and immunohistochemical findings [9-11]. However, it must be pointed out that the risk of progression from histologically malignant lesions to clinical disease with actual morbidity and risk of metastases in these patients is unknown. An international Disorders of Sex Development registry that currently exists will hopefully offer greater insights on the long-term morbidity and mortality associated with malignancies in these patients [11].

The evidence available on 45,X/46,XY patients suggests that no correlation exists between the clinical phenotype and the degree of mosaicism [4,5,7]. The pubertal course, the fertility outcome and the tumor risk seem to be predicted more by degree of genital ambiguity and gonadal differentiation than by the blood/gonadal karyotype [4,5,7]. However, most patients, including mild cases without genital ambiguity and those starting puberty spontaneously, will develop some testicular

impairment in adolescence or young adulthood [7]. In our case, the preserved gonad maintained sufficient Leydig cell function to induce puberty, but the current hormonal profile possibly suggests declining testicular function, raising concerns for future fertility.

Growth seems to be consistently impaired in these patients [7]. Variable outcomes have been reported on GH treatment with a recent review concluding that, although there may be some short- to mid-term improvement in growth, long-term data on adult height are disappointing [12]. However, supraphysiological GH doses and earlier commencement might result in better outcomes, as could have possibly been the case in our patient. Since fibroblasts have the same mesenchymal origin as chondrocytes and osteoblasts, karyotype from skin fibroblasts could be more useful than the blood karyotype to predict the growth phenotype of these patients [12]. Furthermore, periodic screening for cardiac and autoimmune complications should be considered in 45,X/46,XY patients [13,14].

Our case report highlights that 45,X/46,XY mosaicism may present with a very mild phenotype and a normal blood karyotype. Cases without genital ambiguity can be easily missed. However, short stature and decline in testicular function over time are common features, even in mild cases, and these patients also exhibit a significant risk of tumors and infertility. An early diagnosis of gonadal dysgenesis is therefore important in all cases to optimize growth, puberty and fertility outcomes, and to monitor for the increased tumor risk.

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Figure 1. Patient's growth pattern and pubertal progression.

Table 1. Serial hormonal profiles.

	2.00y	**11.50y**	**13.16y**	**15.00y**	**15.98 y**	**Reference ranges**
Testosterone nmol/L	<0.69	<0.69	<0.69	1.44	11.00	[&]Prepubertal: <0.5 Adult: 10-30
LH IU/L	< 0.7	<0.2	0.9	2.5	4.6	[&]Prepubertal: <0.5 Tanner stage 2: 1-4 Tanner stage 4: 2-8
FSH IU/L	0.5	0.8	1.7	10.8	19.3	[&]Prepubertal: 0.4-1.6 Tanner stage 2: 0.5-4.0 Tanner stage 3: 2.5-4.5 Tanner stage 4: 3.0-5.5
Inhibin B pg/mL			229.4	47.7		[#] 12-17 years: 74-470
AMH pmol/L			353.5	65.0		[*]Tanner stage 3: 18 – 587 Tanner stage 4: 12 - 90
Tanner stage	G1,P1,A1	G2,P1,A1	G3,P2,A1	G4,P2,A1	G5,P3,A1	
Left testicular volume (ml)	2	3	8	12-15	15-20	

y: years; m: months; G: genitalia stage, P: pubic hair stage, A: axillary hair stage, AMH: Anti-mullerian hormone

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