An XY female with Müllerian duct development and persistent Wolffian duct structures

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Summary

Disorders of sexual differentiation are usually diagnosed at an early age. We hereby describe a case of a 29-year-old phenotypic woman who during the evaluation of amenorrhea was found to have a 46, XY karyotype. Further evaluation (including laparoscopy) suggested that she presented a variant of gonadal dysgenesis, with the particularity of having well-developed müllerian structures and testicular remnants alongside a steroid-producing gonadoblastoma.

Key words: Laparoscopy; Gonadoblastoma; Male karyotype; Müllerian ducts; Genitalia.

Introduction

Primary amenorrhea is usually the result of a genetic or anatomic abnormality. A case of a phenotypic woman with a 46, XY karyotype and well-developed müllerian structures is presented.

Case report

A 29-year-old, phenotypically normal caucasian postpubertal woman with primary amenorrhea was referred for endocrine evaluation.

She reported that at age 13, normal breasts, as well as pubic and axillary hair had developed. However, by age 17 menses had not appeared. Evaluation at this age included pelvic ultrasound, which showed the presence of the uterus (3.3 x 1.8 x 2.4 cm) and of the ovaries (left: 3.1 x 1.2 x 2.4 cm and right: 2.2 x 1.3 x 2.1 cm); small follicles were described in both ovaries. At that time hormonal evaluation showed normal luteinizing hormone and elevated follicle-stimulating hormone (Table 1). She underwent laparoscopy and ovarian biopsy, the latter not disclosing typical ovarian parenchyma. Chronic treatment with conjugated estrogens and cyclic administration of medroxyprogesterone (HRT) resulted in regular menses. Normal female sexual activity was reported. Family history was unremarkable.

The patient was 174 cm tall, weighed 70 kg and was unequivocally of female habitus. The breasts were well developed; galactorrhea was not noted. Axillary and pubic hair was normal. Acne was not present. Blood pressure was 110/80 mmHg. Cardiac auscultation disclosed a systolic murmur on the apex. Pelvic examination was normal and clitoromegaly was not noted. On transvaginal ultrasound the uterus was normal (4.1 x 3.5 x 2.3 cm) and the adnexa were atrophic (left: 2.2 x 1.0 and right: 1.8 x 0.9 cm, the latter was reported as streak-like). HRT was discontinued and after one month the hormonal work-up showed elevated estradiol and high-normal testosterone serum levels. Serum progesterone and 17-OH progesterone corresponded to the follicular phase. Basal gonadotrophins were elevated and an adequate response to 100 μg IV of gonadotrophin releasing hormone was elicited (Table 1). The karyotype was 46, XY. Further molecular analysis of the Y chromosome, using the polymerase chain reaction for the amplification of SRY, ZFY (short arm) and DYZ1 (long arm) loci, revealed a normal SRY gene as well as normal-sized ZFY and DYZ1 regions.

On laparoscopy, fully developed female genitalia of normal appearance were found. The uterus was of normal size and position. The fallopian tubes and the gonads were removed. The fal-

Table 1. — *Hormonal evaluation.*

Hormone (units; normal range)	At age 17 Basal values	At age 29 Basal values	After 100 μg GnRH IV	Postoperatively, 6 weeks with no HRT
Free Testosterone (nmol/l; 0.48-2.64)	0.69	2.3		0.12
DHEA-S (micromol/l; 0.95-11.70)		8.42		5.4
17-OH-Progesterone (nmol/l; 0.30-3.63)		1.6		2.2
Estradiol (nmol/l; follicular phase: 0.07-0.67)		1.4		< 0.07
Progesterone (nmol/l; follicular phase: 0.48-4.45)		2		1.13
Luteinizing Hormone (mU/ml; follicular phase:1.9-8.0)	5	35.5	132.7	38.5
Follicle Stimulating Hormone (mU/ml; follicular phase: 2.4-9.3	11	94.8	133.2	125

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lopian tubes were 7.0 x 0.5 cm and 4.0 x 0.4 cm on the left and right side, respectively, and of normal histology. The left ovary had a mean diameter of 2.0 cm, contained a lobular mass, and on microscopic examination was shown to be a gonadoblastoma without evidence of malignant transformation. The right ovary was 1.5 x 1.0 x 0.3 cm, with no primordial follicles present. However, at the hilus, epididymis and vas deferens structures were noted.

Six weeks postgonadectomy – withholding HRT – the gonadotropins were elevated while the sex steroids were low (Table 1). The patient was treated again with HRT.

Discussion

Our patient presented with unusual features. Although of female phenotype, she had a male karyotype, with a presumably normal Y-chromosome; the müllerian structures were well developed. Measurement of serum antimüllerian hormone (AMH) was not implemented since at postpubertal age the diagnostic yield of such measurements is limited with AMH being uniformly low [1]. In our case only the XY karyotype was compatible with the androgen insensitivity syndrome (AIS) [2]. Normal female external genitalia were found, however, as is the case in true hermaphroditism, epididymis and vas deferens were found in the right ovary. The fallopian tubes were normal, while in hermaphrodites fallopian tubes adjacent to testicular tissue are blind, under- or undeveloped, as a result of the local action of AMH. [3]. Vanishing (regressing) testis syndrome occurs in 46, XY individuals who may appear as females [4]; abnormalities are demonstrated in the short arm of the Y-chromosome by Y-DNA hybridization studies. The presence of normal SRY and the ZFY loci in this patient seems at variance with this diagnosis (although the role of the ZFY gene on testicular feminization may be contested) [5]. On the other hand it may be suggestive of possible alterations within other – important for sex determination – loci such as the SOX9 gene, thus explaining the sex reversal observed. Persistent müllerian duct syndrome, although characterized by the presence of functional testes and müllerian structures, is not a likely diagnosis as it is encountered in phenotypic males [6].

Early surgical removal of testicular remnants is advocated, considering the high risk (30%) of developing gonadal tumors (gonadoblastomas or dysgerminomas) [7]. Laparoscopic evaluation followed by gonadectomy has been applied in cases of gonadal dysgenesis [8], AIS [9] and male pseudohermaproditism [10] and is a valid and effective procedure in the management of analogous cases.

This patient seems to be a case of XY gonadal dysgenesis, with variation, due to the gonadoblastoma in the left gonad. The phenotype apparently is the result of a concomitant lack of synthesis and secretion of both AMH and testosterone during early embryonal life. The observed gonadotrophin levels at late adolescence were probably the result of an immature hypothalamic-pituitary-gonadal axis. The elevated serum estradiol and the high-normal testosterone levels measured at a later age could be due to production of these steroids by the patient's gonadoblastoma [11]. Corroborating this, in our subject, the removal of the gonadoblastoma resulted – postoperatively – in low serum sex steroids.

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