# XY gonadal dysgenesis – development of a germ cell tumor: case report

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**Summary**

Gonadal dysgenesis (GD) is a rare congenital malformation that affects about one in 3,000 births. The authors present a case of a 17-year-old woman with primary amenorrhea and poor breast development. They conducted a laparoscopic surgery and bilaterally removed hypoplastic streak gonads. Histopathology of the ovaries revealed bilateral streak gonads with gonadoblastomas and a right-sided dysgerminoma.

*Key words:* 46XY karyotype; Gonadal dysgenesis; Gonadoblastoma.

## Introduction

Gonadal dysgenesis (GD) is a genetically caused heterogeneous disorder of the reproductive system that affects about one in 3,000 births [1-3]. A complete form can be differentiated from a partial form of XY-GD. The complete loss of primordial germ cells in developing gonads of an embryo leads to extremely hypoplastic (underdeveloped) and dysfunctioning gonads, mainly composed of fibrous tissue [4]. Complete GD is therefore characterized by hypergonadotropic hypogonadism, female external genitalia, and streak gonads consisting only of fibrous stroma without hormonally active tissue, such as Sertoli cells. The development of Müllerian derivatives like fallopian tubes, uterus, and vagina are not impaired, because of the absence of the anti-Müllerian hormone (AMH). Clinically the complete form is characterized by primary amenorrhea and absence of breast development [5, 6].

In contrast to the complete form, endocrine active tissue can be present in partial XY-GD. The androgen production from Leydig cells induces the differentiation of the Wolffian ducts into seminal vesicles, epididymis and vasa deferentia. Most frequently the AMH production by Sertoli cells is partially impaired causing a coexistence of Wolffian and Müllerian ducts [5, 7].

## Case Report

### *Medical history*

The authors present a case of a 17-year -old girl with primary amenorrhea and poor breast development. Inconspicuous female phenotype, normal growth, and psycho-social development corresponded to her age. There was no reported history of hormonal intake, cyclical pain, exposure to radiation, cytostatic therapy or any nervous system symptoms. Furthermore there was no history of relevant trauma or surgical procedures. She is the first child of a non-consanguineous marriage and her mother's age at time of delivery was 28 years. Her family medical history was inconspicuous.

### *Diagnostics*

Physical examination: 165 cm tall female, weighing approximately 59 kg. No evidence of acne, hirsutism, acanthosis nigricans, goiter or cushingoid stigmata. Breasts were small and poorly-developed with hypopigmented areola (Tanner's Stage II). External genitalia showed a female phenotype, with no evidence of clitoromegaly. Further examination revealed intact hymen. Vagina and cervix were small and hypoplastically developed (Figure 1).

Laboratory tests: hypergonadotropic hypogonadism, AMH 0.5 ng/ml (–), follicle-stimulating hormone (FSH) 57.4 mU/ml (+), luteinizing hormone (LH) 32.4 mU/ml (+), 17β-estradiol < 5 pg/ml (–), dehydroepiandrosterone sulfate (DHEAS) 260 µg/ml (=), prolactin 309 mIU/l (=), testosterone 0.13 ng/ml (=), androstenedione 0.9 ng/ml (–).

Transvaginal ultrasonography of the pelvis showed a small and hypoplastic uterus; ovaries were not detectable (Figure 2).

Genetic investigation: The karyotype showed an inconspicuous male 46 XY genome, SR-Y and SF-1 locus without pathological findings.

### *Therapy*

The patient was admitted to this present hospital and the authors conducted an operative laparoscopic procedure under general anesthesia. The laparoscopy revealed a hypoplastic uterus, inconspicuous fallopian tubes, and streak gonads on both sides. They performed a bilateral gonadectomy. The histopathology of the excised gonads showed bilateral gonadoblastomas with an 11-mm dysgerminoma on the right side.

The authors conducted two cycles of cytostatic therapy with cisplatin/etoposid according to the MAKEI 96 protocol. The cytostatic treatment was well-tolerated by the patient. Subsequently a hormone replacement therapy was initiated with cyclo-progynova. After the first cycle of hormonal treatment, menstruation initiated and breast growth increased.

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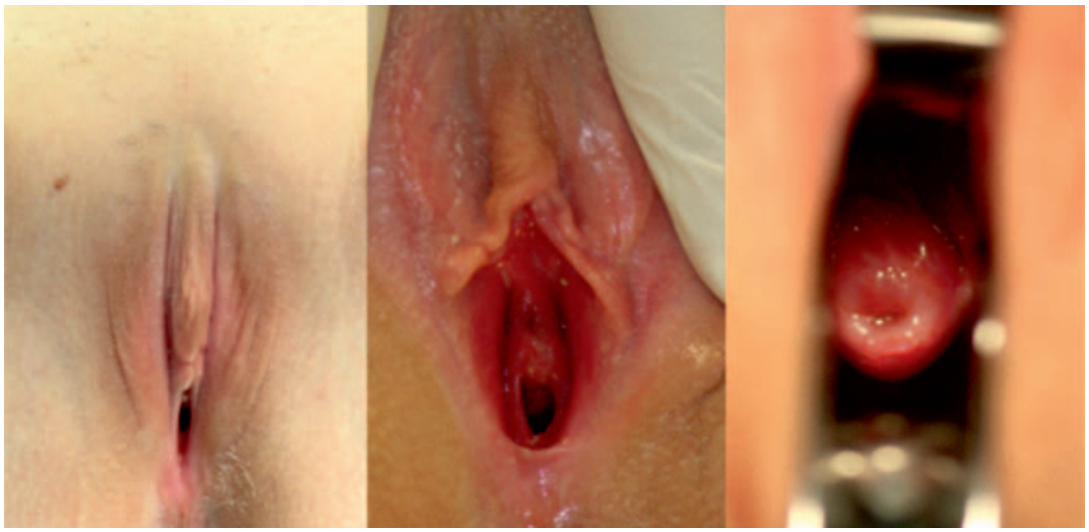

Figure 1. — Infantile external genial, vagina, and cervix existent but hypoplastically developed.

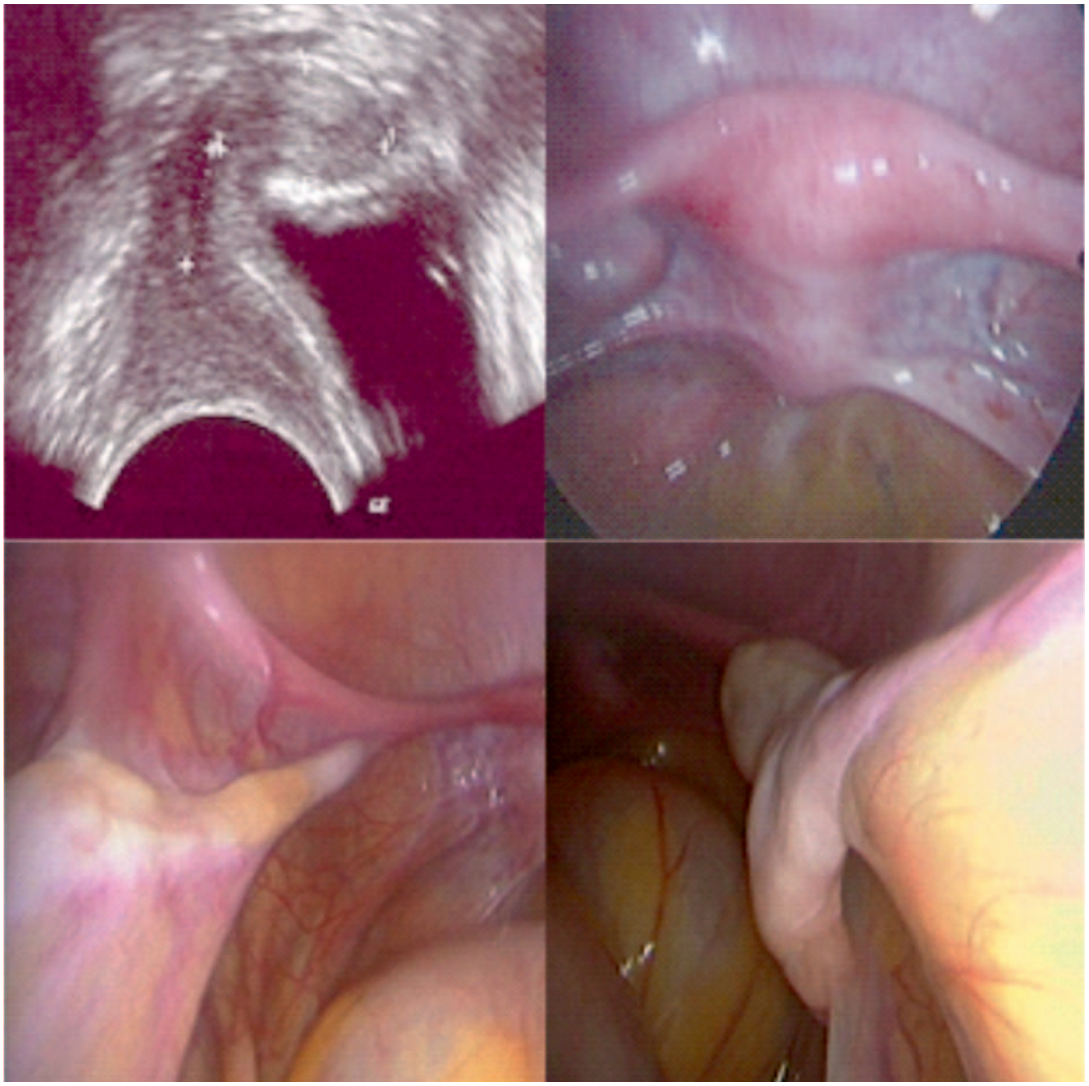

Figure 2. — Vaginal sonography of the hypoplastic uterus (upper left). Images from the endoscopy reveal a very small uterus and bilateral streak gonads (upper right, bottom left and right).

## Discussion

The patient suffers from a male pseudohermaphroditism: female phenotype and male genotype. Wieacker suggested in 2003 the following diagnostic algorithm: the existence of Müllerian structures like the upper 2/3 of the vagina, uterus, and fallopian tubes indicates the lack of AMH production during embryonic development. This is the case in the complete XY-GD. The lack of these structures however leads to the existence of AMH producing Sertoli-cells. The differential diagnosis includes different disturbances of the steroid hormonal synthesis, androgen insensitivity or a defect in the LH receptor. The diagnosis of an agonadism is difficult (e.g. vanishing testis). In this case variable forms of the external and internal genital variations are possible according to the time point of testicular regression during embryonic development [8].

The development of the testis is a strictly regulated process. Variable genes are involved: SRY-gene (sex-determining-region Y, induces Sertoli-cells (AMH)), SF-1 (steroid genic factor 1, early development of the gonads, AMH-expression), DHH (desert hedgehog, Leydig-cell-differentiation (testosterone), spermatogenesis) [1]. Different mutations in this signaling cascade cause variable forms of the external and internal genital.

The incidence of malignant gonadoblastoma in patients with dysgenetic gonads is about 30% [5]. Therefore a prophylactic, bilateral gonadectomy is recommended before the onset of puberty. The response rate to chemotherapy is excellent. Five-year survival rate: 100% / 85% / 79% / 71% (Stage I-IV). Seven-year survival rate: 96% at FIGO Stage I (MAKEI-96).

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