Ochsner Journal XX:1–5, 2026
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DOI: 10.31486/toj.26.0027

Swyer Syndrome With Coexisting Germ Cell Neoplasia In Situ and Gonadoblastoma

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Background: Swyer syndrome—46,XY complete gonadal dysgenesis—is characterized by defective gonadal development and manifests as primary amenorrhea and poor breast development in an unambiguous female. Individuals with complete gonadal dysgenesis harbor streak abdominal gonads and are at high risk of developing germ cell tumors, including germ cell neoplasia in situ, gonadoblastoma, and dysgerminoma.

Case Report: A 15-year-old patient born of a nonconsanguineous marriage and assigned female at birth presented for evaluation of primary amenorrhea. She had spontaneous breast development during the prior year, but her mother perceived the development to be inadequate. On examination, the patient had Tanner stage 3 breast development, unambiguous female external genitalia, and a normal feminine voice. Investigations revealed hypergonadotropic hypogonadism (follicle-stimulating hormone » luteinizing hormone), 46,XY karyotype, normal female-range testosterone, prepubertal uterus, and bilateral abdominal streak gonads, prompting a clinical diagnosis of complete gonadal dysgenesis. Clinical exome sequencing was unremarkable, and fluorescent in situ hybridization did not reveal SRY gene deletion. Considering the increased risk of gonadal malignancy, prophylactic laparoscopic gonadectomy was performed. Histopathology revealed germ cell neoplasia in situ in the left gonad and gonadoblastoma in the right gonad; close follow-up is planned. Hormone replacement with estradiol valerate was initiated, with a plan to monitor pubertal progression, escalate to adult doses over a period of 1 to 2 years, and add progesterone once breasts reach Tanner stage 5.

Conclusion: This case highlights the variability of pubertal development in patients with complete gonadal dysgenesis; the neoplastic potential of dysgenetic gonads; and the importance of early diagnosis, counseling, and multidisciplinary care.

Keywords: *Amenorrhea, breast, disorders of sex development, gonadal dysgenesis–46,XY, gonadoblastoma, neoplasms–germ cell and embryonal*

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INTRODUCTION

Disorders of sex development are congenital disorders characterized by an atypical chromosomal, gonadal, or phenotypic sex. These conditions may or may not be associated with genital ambiguity and are broadly categorized into 46,XX; 46,XY; and sex-chromosome disorders.[1] The group of 46,XY disorders of sex development includes conditions associated with defective gonadal development (such as complete gonadal dysgenesis); defective androgen biosynthesis or action (such as Leydig cell hypoplasia, 17β-hydroxysteroid dehydrogenase type 3 deficiency, steroid 5α-reductase type 2 deficiency, androgen insensitivity syndrome); and other abnormalities (such as persistent Müllerian duct syndrome).[1]

Swyer syndrome—46,XY complete gonadal dysgenesis—is a rare condition with a reported incidence of 1 in 80,000 live births.[2] Complete gonadal dysgenesis results from defective gonadal development in the fetus and most often presents in adolescence with primary amenorrhea and poor breast development. Although rare, spontaneous breast development and even menstruation have been described in patients with complete gonadal dysgenesis.[3-5] Individuals with complete gonadal dysgenesis harbor streak abdominal gonads that are at an increased risk of developing germ cell tumors. The risk ranges between 15% and 60%, and prophylactic gonadectomy is recommended at the time of diagnosis.[6,7]

We present the case of a teenaged female with complete gonadal dysgenesis who manifested spontaneous breast development and nonfunctioning gonads with germ cell neoplasia in situ in the left gonad and gonadoblastoma in the right gonad.

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CASE REPORT

A 15-year-old patient assigned female at birth presented to our outpatient department for evaluation of primary amenorrhea. She was born of a nonconsanguineous marriage. No genital ambiguity was noted at birth, and she had an uneventful childhood. The patient's mother noticed breast development during the prior year but perceived the development to be inadequate. The patient denied the use of exogenous sex steroids. She had no history of cyclical abdominal pain, inguinal or labial swellings, hernia, or pubertal virilization. Gender identity and social role were consistent with the female sex.

Examination revealed a young female with normal vital signs, height of 160.5 cm (+0.38 standard deviation score for females and –0.72 standard deviation score for males), weight of 57.1 kg, and body mass index of 22.2 kg/m^2. Midparental height was 163.5 cm for a female and 176.5 cm for a male child. The upper segment to lower segment ratio was 0.84, and the arm span was 168 cm. Sexual maturity rating revealed Tanner stage 3 breast and Tanner stage 3 pubic hair development, with scant axillary hair. The patient had a normal feminine voice and unambiguous female external genitalia. External masculinization score was 1/12, and Prader score corresponded to stage 0. Complete blood count, liver function tests, kidney function tests, and routine urine examination were normal. Hormonal investigations revealed hypergonadotropic hypogonadism (Table) and karyotype was 46,XY (Giemsa banding; 30 cells analyzed). Bone age corresponded to 13 years in a female child and 14 years in a male child, according to the Greulich and Pyle method.

Given primary amenorrhea in an unambiguous female with a 46,XY karyotype, we considered the following differentials: (1) complete gonadal dysgenesis, (2) complete androgen insensitivity syndrome, and (3) androgen biosynthetic defects such as Leydig cell hypoplasia. The pattern of gonadotropin elevation (follicle-stimulating hormone » luteinizing hormone, with predominant luteinizing hormone elevation expected in complete androgen insensitivity syndrome and Leydig cell hypoplasia); low anti-Müllerian hormone levels (often normal or elevated in complete androgen insensitivity syndrome and Leydig cell hypoplasia); and female-range testosterone levels (elevation to male range in complete androgen insensitivity syndrome) clearly favored complete gonadal dysgenesis vs other etiologies. The patient's neuropsychological assessment, electrocardiography, echocardiography, and pure-tone audiometry (to evaluate for organ dysfunction associated with gonadal dysgenesis) were normal.

Magnetic resonance imaging (MRI) of the pelvis revealed a prepubertal uterus measuring 14 × 47 × 32 mm, maintained endometrial-myometrial differentiation, endometrium thickness of approximately 3 mm, and a corpus to cervix ratio <1. Bilateral streak gonads were noted in the region of the ovarian fossa (Figure 1). Clinical exome sequencing did not reveal any pathogenic variant in genes known to cause gonadal dysgenesis (eg, SRY, NR5A1/SF1, SOX9, MAP3K1, WT1, DHH, DMRT1, ATRX, GATA4). Fluorescence in situ hybridization performed to look for large SRY [Yp11.3] deletion revealed a 46,XY karyotype with the presence of the SRY gene. Thus, the genetic workup was negative for the common causes of complete gonadal dysgenesis.

Table. Hormonal Parameters of the Patient

Parameter	Value	Reference Range
Triiodothyronine, ng/mL	1.72	0.35-1.93
Thyroxine, μg/dL	6.88	5.0-12.0
Thyroid-stimulating hormone, μIU/L	1.34	0.35-4.94
Cortisol 0800 h, μg/dL	12.8	6.0-18.4
Dehydroepiandrosterone sulphate, μg/dL	117.2	45.1-385
β-human chorionic gonadotropin, IU/L	< 1.2	<5
Lactate dehydrogenase, U/L	203.5	< 220
Alpha-fetoprotein, ng/ml	2.84	<8.78
Luteinizing hormone, IU/L	19.1	1-12 (follicular phase)
Follicle-stimulating hormone, IU/L	100.6	3.0-8.1 (follicular phase)
Estradiol, pg/mL	<10	Tanner stage 1: UD-20 2: UD-24 3: UD-60 4: 15-85 5: 15-350
Prolactin, ng/mL	10.31	3-30
Testosterone, ng/dL	26.5	Tanner stage 1: <7-20 2: <7-47 3: 17-75 4: 20-75 5: 12-60
Anti-Müllerian hormone, ng/mL	0.21	0.62-7.8 (female, 15 years)
Urine routine microscopy	Normal	

UD, undetectable.

The patient and her family were informed regarding the nature of the disorder and the need for bilateral gonadectomy. Future fertility options in the form of an ovum donation pregnancy were also discussed. The patient underwent laparoscopic gonadectomy, and the streak gonads were removed through the 10 mm central port in an endobag. Histopathology suggested germ cell neoplasia in situ in the left gonad (Figure 2) and gonadoblastoma in the right gonad (Figure 3).

The patient's postoperative course was uneventful, and at week 4, she began hormone replacement therapy with estradiol valerate (1 mg per day), with a plan to monitor pubertal progression, escalate to adult doses over a period of 1 to 2 years, and add progesterone once her breasts reach Tanner stage 5.

DISCUSSION

Typically, patients with complete gonadal dysgenesis have bilateral nonfunctional streak gonads, manifest hypergonadotropic hypogonadism, and have poor breast development during puberty.[8] However, spontaneous partial breast development as in our case has been reported in

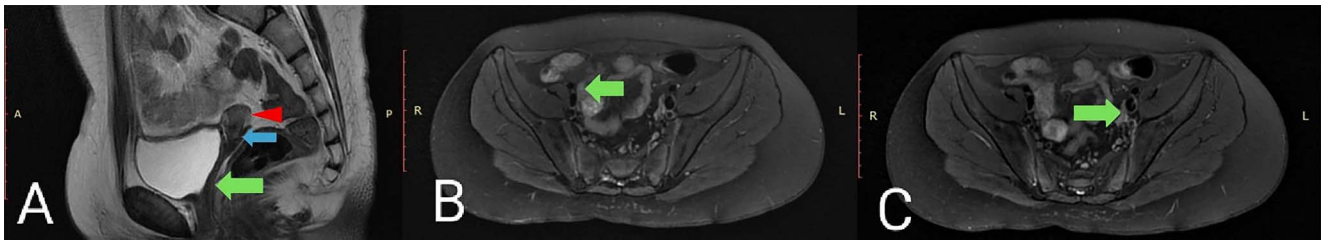

Figure 1. (A) T2 sagittal magnetic resonance image of the pelvis shows a small prepubertal uterus (corpus [red arrowhead], cervix [blue arrow]), a corpus to cervix ratio <1, and a vagina (green arrow). (B, C) T2 fat-suppressed axial views show bilateral streak gonads (green arrows).

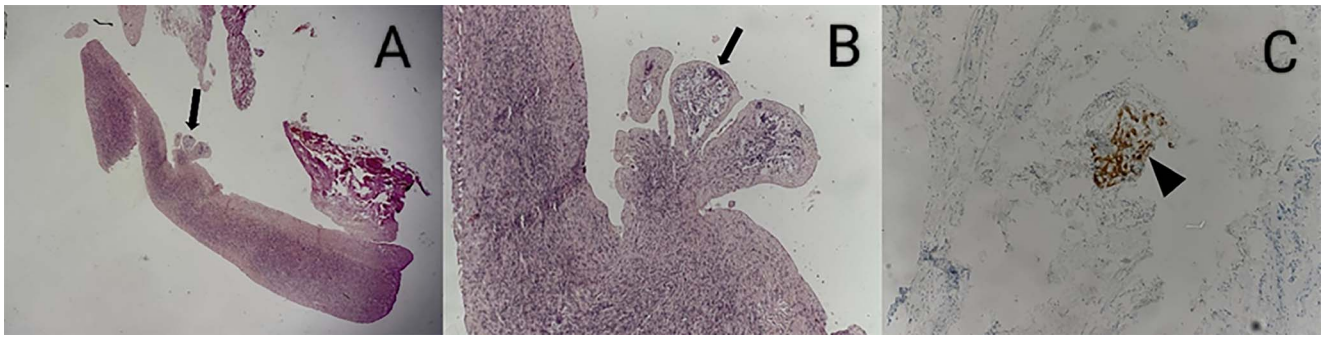

Figure 2. Photomicrographs of the left gonad with hematoxylin and eosin staining show germ cell neoplasia in situ (arrows) at (A) 20 × magnification and at (B) 50 × magnification. (C) Sex cord stromal cells show positive inhibin B staining (arrowhead).

isolated reports.[3-5] A case series from Latvia reported Tanner stage 2 or more breast development among 4 of 7 patients with complete gonadal dysgenesis.[3] An exceptional case of complete breast development (Tanner stage 5) and spontaneous menstruation has also been reported.[5] Spontaneous pubertal development can mask the diagnosis of gonadal dysgenesis. Multiple theories have been proposed to explain this phenomenon, including estrogen production by the streak gonads,[9,10] aromatization of androgens,[5,11] and increased breast tissue sensitivity to estrogen.[5,11] In addition, gonadoblastoma can produce testosterone and manifest as pubertal virilization.[12]

Patients with gonadal dysgenesis and Y chromosome material are at increased risk of gonadal germ cell tumors, including germ cell neoplasia in situ and gonadoblastoma. Although gonadoblastoma is a benign germ cell tumor, it has the potential for malignant transformation and can progress to an invasive germ cell tumor such as dysgerminoma, teratoma, and embryonal carcinoma.[6] In patients with complete gonadal dysgenesis, the risk of gonadal malignancy has been reported to be as high as 60%, with gonadoblastoma being the most common neoplasm.[6,7] Importantly, imaging modalities such as ultrasonography and MRI cannot reliably detect early-stage neoplasms, and

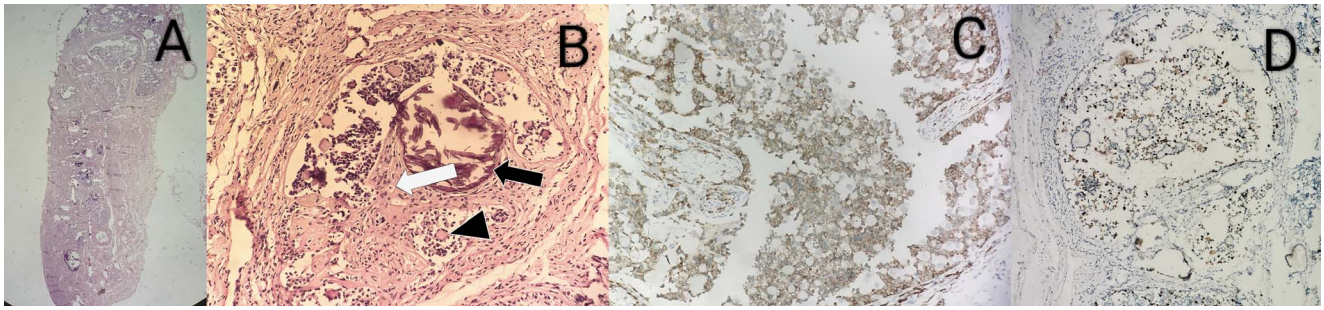

Figure 3. Photomicrographs of the right gonad with hematoxylin and eosin staining show gonadoblastoma at (A) 40× magnification and at (B) 200× magnification, with the tumor comprising well-defined calcified nests (black arrow) intermingled with round to angulated sex cord cells and germ cells (white arrow). Sex cord cells form a palisade at the periphery and are surrounded by a basement membrane deposit (Call–Exner bodies [arrowhead]). (C) Sex cord stromal cells show positive inhibin B staining. (D) Germ cells show positive Ki-67 staining.

tumor markers such as alpha-fetoprotein and human chorionic gonadotropin are insensitive, becoming elevated only in advanced disease and with specific histologic types.[13] For these reasons, any abdominal gonad in a patient with gonadal dysgenesis (complete or partial) that cannot be surgically brought down into the labioscrotal folds should be excised.

The timing of gonadectomy is a matter of debate. As the risk of gonadal malignancy is very low during the prepubertal years, the surgery can be postponed to a later age unless other indications arise.[6,7] A systematic review by Morin et al found that among patients with disorders of sex development, the risk of finding a germ cell neoplasia in situ or germ cell tumor during gonadal surgery increases after age 15, especially between ages 15 and 20 years.[14] Morin et al also found that the 5-year oncologic outcomes among patients with germ cell neoplasia in situ were equivalent to the outcomes of patients without germ cell neoplasia.[14] These data are reassuring in the context of our patient; however, long-term follow-up will be critical.

Gonadal dysgenesis results from a defect in key candidate genes (SRY, NR5A1/SF1, SOX9, MAP3K1, WT1, DHH, DMRT1, ATRX, GATA4) involved in the process of male sex determination (ie, the conversion of bipotential gonads into testes). Among candidate gene defects, inactivating mutations and deletions in the SRY gene located on the short arm of the Y chromosome (Yp11.3) are the most common, accounting for 10% to 20% of all cases of complete gonadal dysgenesis.[6,15] However, despite extensive genetic workup, approximately 50% of cases remain unexplained.[15] These cases are likely related to variants in regulatory elements of genes such as SOX9 that are not detected by current diagnostic strategies but may become evident with the wider use of whole-genome sequencing.[15] In our patient, no pathogenic variant was identified by clinical exome sequencing of candidate genes for XY gonadal dysgenesis. Furthermore, the fluorescence in situ hybridization analysis performed to detect a large SRY gene deletion was noncontributory. However, the clinical, biochemical, and radiologic picture; the 46,XY karyotype; and evidence of germ cell neoplasia in situ and gonadoblastoma on histopathology firmly established the diagnosis of complete gonadal dysgenesis in our patient.

CONCLUSION

Spontaneous pubertal development does not exclude a diagnosis of complete gonadal dysgenesis, and a karyotype should be performed for all patients manifesting hypergonadotropic hypogonadism. Patients with complete gonadal dysgenesis are at high risk for germ cell tumors, especially after age 15 years, and prophylactic gonadectomy should be offered routinely. This case highlights the neoplastic potential of dysgenetic gonads; the variability of pubertal development in complete gonadal dysgenesis; and the importance of early diagnosis, counseling, and multidisciplinary care.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

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