CASE REPORT

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Seminoma in 46, XY Gonadal Dysgenesis: Rare Presentation and Review of the Literature

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What is already known on this topic?

Swyer syndrome is a rare congenital condition that is known to be a risk factor for developing germ cell tumors. 46, XY gonadal dysgenesis (GD) involves a high risk of gonadoblastoma development with malignant potential such that the onset is greatest at or after the event of puberty.

What this study adds?

This study reports a 12-year-old phenotypic female with 46, XY GD, who developed an advanced metastatic seminoma. Furthermore, a review of the literature was performed in order to highlight the rarity of the development of seminoma in the context of 46, XY complete GD.

Abstract

Swyer syndrome is a rare congenital condition that serves as a risk factor for developing germ cell tumors. The condition belongs to the group of 46, XY disorders of sexual development, is characterized by complete gonadal dysgenesis (CGD) and is mostly manifested as delayed puberty and primary amenorrhea during adolescence. Individuals with Swyer syndrome are known to be phenotypically female with normal internal and external female genitalia at birth. 46, XY GD involves a high risk of gonadoblastoma development with malignant potential such that the onset is greatest at or after the event of puberty. This report of a 12-year-old phenotypic female with 46, XY GD, who developed an advanced metastatic seminoma, highlights the rarity of the development of a seminoma in the context of 46, XY CGD.

Keywords: Seminoma, Swyer syndrome, gonadal dysgenesis, 46, XY

Introduction

Disorders of sexual differentiation (DSD) are congenital conditions such that the chromosomal profile, gonadal sex, and phenotypic appearance of the external genitalia of the individual are discordant (1). The broad categories that fall under DSD include 46 XY DSD, 46 XX DSD, ovotesticular DSD, and sex chromosome DSD, for example 47 XXY, 45 X, and 45 X/46 XY. Individuals with 46, XY DSD present with a varied clinical picture, from females with normal external genitalia to under-virilized males (2).

The underlying cause of 46, XY DSD involve gonadal dysgenesis (GD) or dysfunction of the synthesis or action of androgens or anti-Müllerian hormone (AMH) (3). GD,

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previously known as sex reversal (4), can manifest as complete GD (CGD) or partial GD. Disorders of androgen synthesis or action involve various enzymatic defects of testosterone synthesis or conversion and defective androgen receptors such as 17-beta HSD deficiency, 5α-reductase deficiency, and androgen insensitivity syndromes (1,5).

Swyer syndrome, first described by Swyer (6) in 1955, is a type of 46, XY DSD characterized by CGD. The incidence of all cases with 46, XY DSD in general is estimated to be 1:20,000. The incidence of the Swyer syndrome has been estimated to be 1:100,000 (1). The underlying pathology of this condition involves the presence of bilateral, non-functional streak gonads that fail to secrete testosterone and AMH. Therefore, individuals with Swyer syndrome are known to be phenotypically female with normal internal and external female genitalia at birth. The condition most commonly is manifested during adolescence as delayed puberty and primary amenorrhea (7).

Patients with 46, XY CGD have the highest tumor rate among a population of patients with DSD and the presence of a Y chromosome (8). Swyer syndrome involves a high risk of gonadoblastoma development with malignant potential, such that the onset is greatest at or after the event of puberty (9). Gonadoblastomas are *in situ* benign tumors that can transform to malignant germ cell tumors, such as dysgerminoma or seminoma (10). The risk of malignancy is reported as 37% to 45% (11,12). Once the diagnosis of Swyer syndrome is made, the patient should undergo a gonadectomy to prevent the development of gonadal malignancies (13). Furthermore, puberty is induced via estrogen supplementation for the development of secondary sexual characteristics. In the long term, hormone replacement therapy, including estrogen and progesterone, is given to maintain the menstrual cycle (1).

Swyer syndrome is a rare congenital condition that serves as a risk factor for developing germ cell tumors. This report of a 12-year-old, phenotypic female with 46, XY GD, who developed an advanced metastatic seminoma highlights the rarity of the development of a seminoma in the context of 46, XY CGD.

Case Report

A 12-year-old Caucasian phenotypic female with an apparently unremarkable past medical history presented with primary amenorrhea and a large abdominal mass. The patient comes from a non-consanguineous family and both parents and siblings are healthy and have no remarkable past medical history.

One month prior to her admission, the patient's mother noticed a palpable solid mass in the femoral-inguinal region. This gradually increasing palpable abdominal mass was accompanied by pain, abdominal distention, and constipation. The abdominal ultrasound imaging showed an abdominal mass and secondary liver metastasis.

Upon physical examination, her Tanner stage for breast and pubic hair was T1 and T2 respectively. She had palpable lymph nodes at the cervical and right axillary area. Her abdomen was distended, with a palpable and painful mass at the umbilical and left lateral region, with hepatomegaly. She also had a solid palpable mass at the left inguinal region, approximately 4 cm in size, and a smaller one at the right side. Computed tomography of the abdomen revealed a large occupying lesion with patchy inhomogeneous areas and multiple calcifications with diameter of 15x12x8.5 cm. Furthermore, there were blocks of multiple retroperitoneal sizeable masses involving the para-aortic areas, the celiac axis, the liver and bilateral renal hilar areas.

A tumor biopsy was performed, and the findings were morphologically and immunohistochemically compatible with a seminoma.

The patient's seminoma was treated according to the Testicular Cancer Protocol 2011 (14). She completed four cycles of the chemotherapy regimen PEB (bleomycin, etoposide, and cisplatin). After completion of chemotherapy, she underwent bilateral gonadectomy and was given hormonal treatment with estrogens for feminization and later for induction of menarche. She is currently on hormonal replacement therapy with combined estradiol and dydrogesterone. Her growth increased from 150 cm at 13 years to 166 cm at 17 years.

Lab Findings

Hormonal Findings

Pre-operative assessment of gonadal function was performed and the laboratory values demonstrated elevated gonadotrophins (follicle-stimulating hormone 76.25 UI/L, luteinizing hormone 16.08 UI/L), testosterone < 0.02 ng/mL, AMH < 1 pmol/L, inhibin B 10 pg/mL (normal: 10-200 pg/mL) and estradiol levels were < 10 pg/mL.

Genetic analysis was done using whole exome sequencing to check for any mutations that may be associated with the patient's phenotype. A family trio exome analysis (Agilent

exome V8) was employed for better extrapolation of results and possible candidate variants. No clinically relevant variants were detected in the genes tested, but there may be a pathogenic variant or deep intronic modifying mutations outside of the genetic regions of analysis. However, there were two interesting findings involving two genes: *ZNF133* and *COL4A1*. Even though the variations in these two genes are of *de novo* origin, their involvement in the patient's presentation remains unknown. The *ZNF133* gene encodes the Zinc finger protein 133, which is predicted to enable DNA-binding transcription repressor activity and be involved in negative regulation of transcription by RNA polymerase II, along with other functions (15). *COL4A1*, also known as collagen type 4 alpha 1 chain, is a gene found on chromosome 13, and is involved with the formation of the alpha 1 chain of type 4 collagen. This chain is part of a complex protein network that plays numerous roles in the body, such as helping the basement membranes interact with proximal cells, cellular migration, and cellular proliferation (16).

Karyotypic analysis (Agilent) of the bone marrow and peripheral blood revealed the patient to be 46, XY. In addition, fluorescence *in situ* hybridization analysis for *SRY* (sex-determining region Y) was performed revealing a signal pattern of one *SRY* signal and one DYZI, a human Y chromosome specific repeated DNA family, signal in all cells examined.

Tumor markers were investigated prior to the initiation of chemotherapy treatment. The patient had elevated levels of NSE (131.7 ng/mL; reference range: <16.3 ng/mL), CA 125 (209.4 U/mL; reference range: <35 U/mL), and β-hCG (79.33 U/L; reference range: <5 U/L) prior to the initiation of chemotherapy treatment.

Discussion

Swyer syndrome is synonymous with CGD in patients with an XY karyotype. The most widely accepted pathogenic mechanism in this condition is a mutation in the *SRY* gene, which is expressed in the germ cells and Sertoli cells. This gene is known to be responsible for converting the undifferentiated gonads into testes. The mutation leads to the production of a defective protein that does not permit the undifferentiated gonad to develop, resulting in the presence of streak gonads that fail to secrete testosterone and AMH (17). It is estimated that 15% of patients with 46, XY CGD have a mutation in the *SRY* gene (1). Patients with Swyer syndrome typically present with a female phenotype with normal external genitalia and Müllerian structures at birth and usually seek medical care in adolescence for delayed puberty with primary amenorrhea due to the lack of hormonal production by the gonads (7).

Since dysgenetic gonads have a 30% risk of developing a gonadoblastoma, the delayed nature of the diagnosis often results in patients already having developed a germ cell tumor at the time of prophylactic bilateral gonadectomy. A case series of three patients demonstrated the presence of gonadoblastoma in one patient and dysgerminoma in the two other patients incidentally at the time of gonadectomy (18).

Patients with Swyer syndrome are known to be at high risk of developing a germ cell tumor, the commonest example being a gonadoblastoma because they have Y chromosome material in their genome. The risk of developing a germ cell neoplasia in these patients depends on the presence of a region on the Y-chromosome known as the gonadoblastoma (GBY) region (19). Despite being benign tumors, gonadoblastomas have the potential to transform to malignant germ cell tumors in 50% to 60% of cases. Dysgerminomas are reported to be present in 22-66% of the cases (12). A recent study from Latvia demonstrated that gonadoblastomas and dysgerminomas were the most commonly diagnosed tumors in patients with Swyer syndrome and the authors stressed the importance of early diagnosis (20). Furthermore, malignant transformation to seminoma has been reported (21).

Testicular cancer is generally an uncommon type of cancer, forming only 1-2% of all tumors in men. However, it is the most common type of neoplasia among young men (22). Germ cell tumors are the most common type of testicular cancer, such that the occurrence of a seminoma versus a non-seminoma is approximately the same. Risk factors associated with testicular cancer usually arise in patients with undescended testes, a history of testicular cancer, a family history of testicular cancer or GD (22).

The patient reported herein with GD presented with a very rare gonadal tumor.

The development of seminoma in patients with 46, XY GD is very rare with only two previously confirmed reported cases (Table 1). The first case was an 18-year-old female who presented with primary amenorrhea and pelvic masses. She had a seminoma on her right gonad, which was confirmed to be an ovotestis (23). The second case was a 16-year-old female who presented with primary amenorrhea. She had a seminoma on her left gonad, which was confirmed to be

Table 1. The type of tumor reported in patients with Swyer syndrome

Study	Tumor type	Patient age
Alam et al. (9), 2020	Gonadoblastoma/ dysgerminoma	16 years old
Anwar et al. (25), 2021	Dysgerminoma	16 years old
Arafa et al. (26), 2021	Gonadoblastoma/ dysgerminoma	17 years old
Behtash and Karimi Zarchi (27) 2007	Dysgerminoma	20, 19, 17 years old
Ben Temime et al. (28), 2008	Gonadoblastoma/ dysgerminoma	13 years old
Bjersing and Kjellgren (29) 1977	Dysgerminoma or seminoma (not confirmed)	18 years old
Bumbulienė et al. (7), 2020	Gonadoblastoma/ dysgerminoma	9 years old
Çatlı et al. (30), 2015	Gonadoblastoma	15 years old
Chen et al. (23), 2015	Seminoma	18 years old
Dural et al. (31), 2019	Gonadoblastoma/ dysgerminoma	17 years old
Gonzalez-Benitez et al. (32), 2015	Gonadoblastoma/ dysgerminoma	29 years old
Hamed and Hanafy (33) 2021	Gonadoblastoma/ dysgerminoma	19 years old
Han et al. (34), 2011	Dysgerminoma	21 years old
Hanlon and Kimble (18) 2015	Gonadoblastoma/ dysgerminoma	17, 15, 15 years old
Ilter et al. (35), 2008	Gonadoblastoma/ dysgerminoma	26 years old
Jadhav et al. (36), 2006	Gonadoblastoma/ dysgerminoma	19 years old
Jonson et al. (21), 2010	Gonadoblastoma/ dysgerminoma, seminoma	20, 16 years old
Kim et al. (37), 1993	Gonadoblastoma/ dysgerminoma	24 years old
Kumar et al. (38), 2016	Teratoma/dysgerminoma/ yolk sac	14 years old
Milewicz et al. (39), 2016	Gonadoblastoma/ dysgerminoma	18 years old
Stachowicz-Stencel et al. (40), 2011	Choriocarcinoma/ dysgerminoma	14 years old
Yada-Hashimoto et al. (41), 2018	Dysgerminoma	25 years old
Zhu et al. (42), 2011	Dysgerminoma	22 years old
Zhu et al. (43), 2016	Teratoma/dysgerminoma/ yolk sac tumor	16 years old

a streak gonad (21). Our patient would be the third case of seminoma in Swyer syndrome presenting with a palpable pelvic mass to be reported, to the best of our knowledge. A recent cross-sectional multicenter study in 1,040 patients with DSD above the age of 16 years of whom 21 patients had CGD showed that those with CGD had the highest risk (33%) of developing a germ cell neoplasia (24). Among those patients reported in the study, only one patient with CGD had a seminoma.

The work of Elzaiat et al. (3), 2022 demonstrated the most recent genetic basis of 46, XY GD. There seems to be an extensive list of genes and proposed candidates that are associated with the 46, XY GD phenotype, including *SRY*, *SOX9*, *DMRT1*, and *DHH*. *SRY* activates the expression of *SOX9*, a downstream effector that's responsible for Sertoli cells formation. Testis development control can be achieved by the close binding between DMRT1 and SOX9 on target genes in the fetal testis (3). DHH is a protein expressed by Sertoli cells that is responsible for genetic regulation in Leydig cells as well as peritubular myoid cells (2). Figure 1 illustrates a simplified schematic of how the different genes interact. Mutations in this molecular pathway have been shown to be associated with 46, XY CGD (3). In the presented patient, current genetic testing failed to identify the genetic defect associated with her condition, highlighting the need for further experimentation. In the future technological advances in molecular methodologies, such as whole genome sequencing, optical genome mapping and next-generation cytogenetics may aid in elucidating pathogenesis and prognosis of this disorder.

Conclusion

Due to a scarcity of reported cases, we present a very rare case of a patient with Swyer syndrome who developed an advanced metastatic seminoma. Despite the metastatic nature of the seminoma and the symptomatic presentation of the patient, she achieved a good overall outcome after undergoing chemotherapy, bilateral gonadectomy and feminization therapy. This case report and the limited literature included in this review highlight the rarity of a seminoma and the importance of early detection of Swyer syndrome with a subsequent earlier prophylactic bilateral gonadectomy and meticulous follow-up to prevent the development of gonadal malignancy in this group of patients.

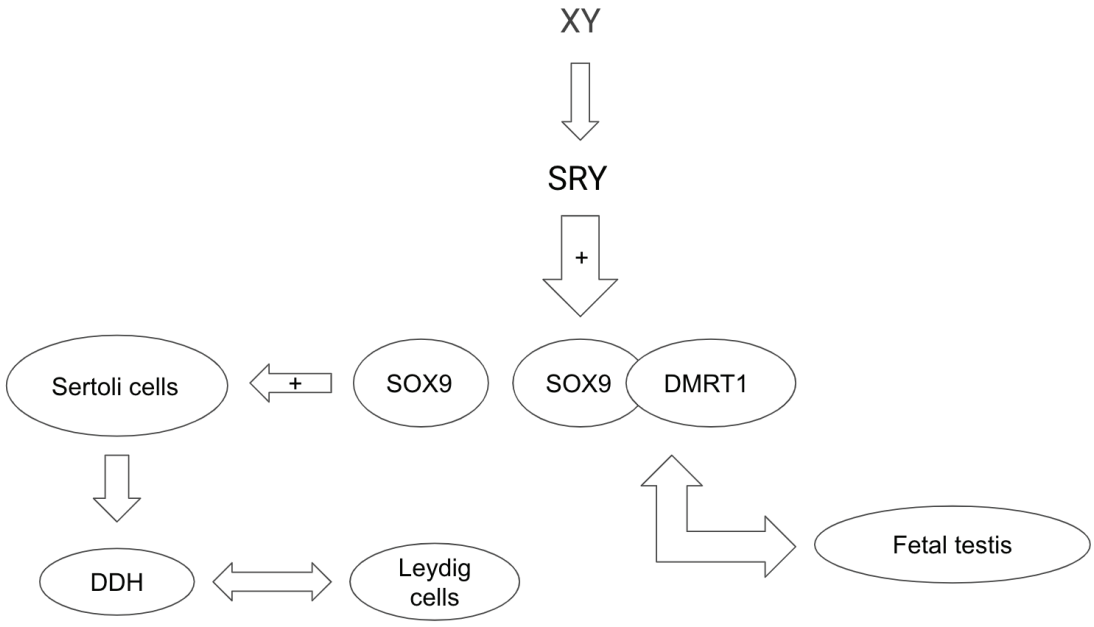

Figure 1. Simplified pathway of the genes regulating testicular differentiation

The *SRY* gene (found on Yp11.3) activates the expression of *SOX9* (found on 17q24.3), which is responsible for the formation of Sertoli cells and regulation of testis development via close binding with DMRT1.

DMRT1 (found on 9p24.3) regulates testis development via close binding with SOX9.

DDH (12q13.12) is responsible for development of the Leydig cells during fetal life.

Ethics

Informed Consent: Informed consent was obtained from those included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Antri Miltiadous, Evangelia Karaoli, Eleni Papachristodoulou, Katerina Nicolaou, Loizos Loizou, Nicos Skordis, Petroula Gerasimou, Concept: Hayato Nakanishi, Maamoun Adra, Nicos Skordis, Petroula Gerasimou, Design: Hayato Nakanishi, Maamoun Adra, Nicos Skordis, Petroula Gerasimou, Data Collection or Processing: Evangelia Karaoli, Eleni Papachristodoulou, Hayato Nakanishi, Loizos Loizou, Maamoun Adra, Nicos Skordis, Literature Search: Hayato Nakanishi, Maamoun Adra, Nicos Skordis, Writing: Hayato Nakanishi, Maamoun Adra, Nicos Skordis, Petroula Gerasimou.

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