Swyer syndrome: A case of primary amenorrhea in an 18-year-old with gonadal mixed germ cell tumor*

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ABSTRACT

An 18-year-old, G0, with primary amenorrhea consulting because of a rapidly enlarging abdominal mass was diagnosed with Swyer syndrome or 46 XY pure gonadal dysgenesis and subsequently underwent staging laparotomy for mixed germ cell tumor (dysgerminoma and yolk sac tumor) arising from her dysgenetic gonad. Bleomycin, etoposide, cisplatin regimen for three to four cycles was planned but the patient was lost to follow-up. A prompt evaluation of her amenorrhea and a timely gonadectomy could have averted the development of malignancy.

Keywords: amenorrhea, gonadal dysgenesis, Swyer syndrome, mixed germ cell tumor of ovary

INTRODUCTION

The early diagnosis and treatment of primary amenorrhea can prevent the unfortunate occurrence of gonadal malignancy especially in individuals with a Y chromosome. Such is the lesson exemplified in this case of an 18 year old with primary amenorrhea and an abdominal mass, diagnosed as Swyer syndrome or 46 XY pure gonadal dysgenesis, who underwent total abdominal hysterectomy and bilateral gonadectomy for FIGO Stage IIB mixed germ cell tumor (dysgerminoma and yolk sac tumor). This report discusses the diagnostic workup and the wholistic management of Swyer syndrome with a gonadal malignancy that would have been preventable.

CASE PRESENTATION

The patient is an 18 year old, single, nulligravid from Samar, who complained of hypogastric mass of three months, initially without accompanying symptoms. However, one month prior to consult, sudden abdominal enlargement was noted, this time with weight loss and early satiety. This prompted consult at our in institution.

She had her thelarche at 15 years of age, pubarche at 16 years of age, but no menarche followed. Past medical history, family, personal and social history were unremarkable. She is a high school graduate, the eldest and the only one with this condition in her family. She was never employed but prefers to stay home and do household chores. She never had any sexual partner although she verbalized that she is "attracted to her female friends".

She is 154 cm tall, weighed 106 pounds, and has a body mass index of 20.2 k/m2 (Figure 1). Breasts are compatible with Tanner stage III. (Figure 2). Axillary hair is sparse. The abdomen is globular with an abdominal girth of 74 cm, with normoactive bowel sounds, dull on percussion on the central abdomen, tympanitic on the dependent areas, with a pelvoabdominal mass measuring 18 x 17 x 7 cm, ovoid, irregularly shaped, solid consistency, nontender, and with limited mobility. Pubic hair corresponds to Tanner stage III. Hymen is intact. Clitoris measures 0.5 x 0.5 cm (Figure 3). On rectal examination, the cervix is small, and the uterus infantile. A solid, non-tender mass located superior to the uterus, which seems to be the inferior pole of the pelvoabdominal mass can be

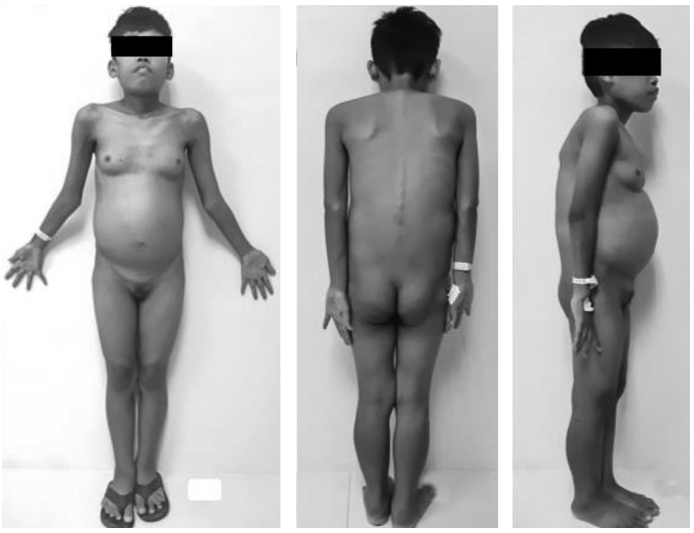

Figure 1. Anthropometric of patient

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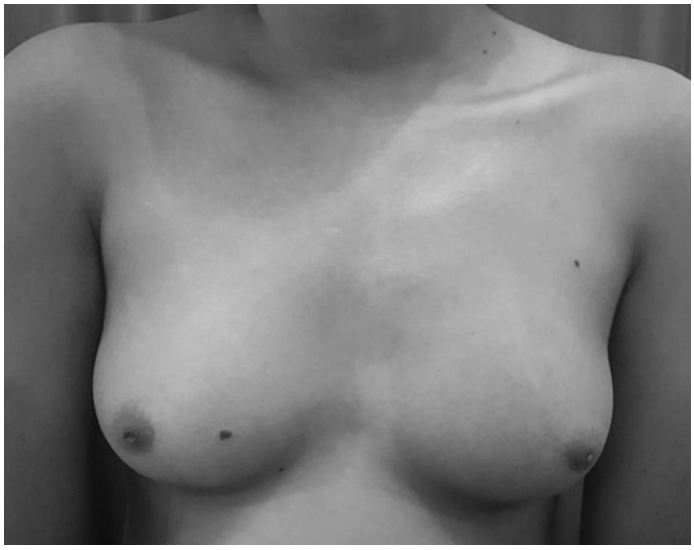

Figure 2. Breast reveals no gross lesions on the breast. Nipples and areolas are elevated and form an edge towards the breasts, corresponding to Tanner stage

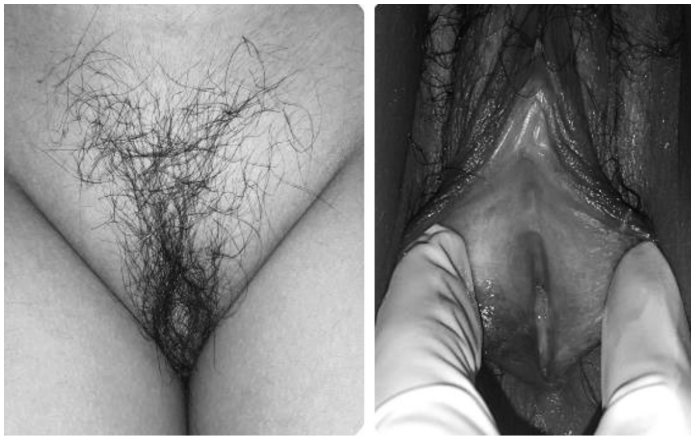

Figure 3. Normal pubic hair is darker, coarser and curlier and spreads sparsely over the skin around the vaginal lips corresponding to Tanner stage III. Vaginal s and canal are both present

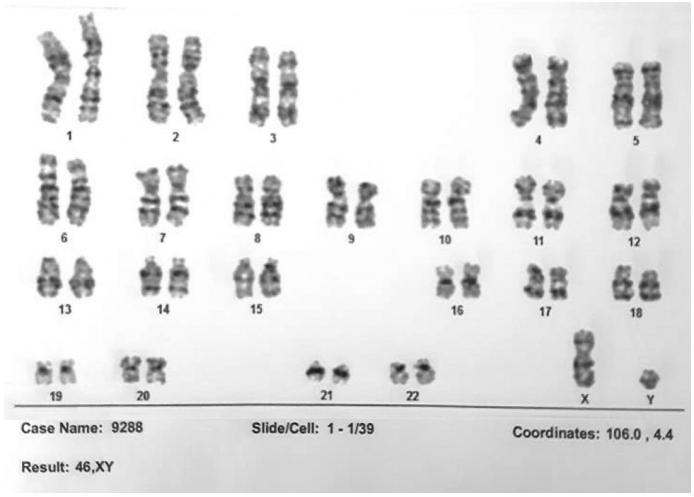

Figure 4. Karyotype of 46 XY, Male

felt. The initial impression was Primary amenorrhea with ovarian new growth probably malignant. Results of the workup showed the following:

Pregnancy test: Negative

Karyotype is 46, XY (Figure 4)

Follicle stimulating hormone (FSH) was elevated at 35.8 mIU/ml (normal: 2.8 to 11.3 mIU/ml)

Serum testosterone was low at 0.025 mg/dL (normal for women: 0.06 to 0.082mg/dL).

Alpha feto-protein was elevated at >1000 IU/ml (0-5.8 IU/ml).

Cancer Antigen-125 and Cancer Antigen 19-9 were within normal values.

Transrectal ultrasound result: Anteverted uterus measuring 2.82 x 2.37 x 3.68 cm. There is an irregular solid mass on the left adnexa measuring 19 x 16 x 10 cm with minimal color on flow mapping (Figure 14). The endometrium was thin measuring 0.38 cm.

No fluid in the cul de sac.

Ultrasound impression: ovarian new growth with non-benign sonologic features vs a pedunculated subserous myoma.

With the finding of a rapidly enlarging abdominal mass with elevated alpha fetoprotein and malignant features on ultrasound in a 46 XY individual with primary amenorrhea and hypergonadotropic hypogonadism, a diagnosis of Swyer Syndrome with gonadal malignancy was made. She was admitted for staging laparotomy.

Intraoperatively, there was a left gonadal mass, solid, multilocular, intact capsule, thick-walled and hypervascularized (Figure 5). It was twisted thrice at the uteroovarian ligament but not gangrenous. Cut section of the mass showed a solid, cream to dark red parenchyma with multiple areas of necrosis and hemorrhage. The uterus was infantile, measuring 4 x 3 x 1 cm (Figure 6). The right gonad was whitish and fibrotic and measured 2 x 0.5 cm. Fallopian tubes were normal. There were tumor implants measuring 0.2 x 0.2 cm on the posterior cul-de-sac. There was no ascites. A complete cancer staging (peritoneal fluid cytology, total abdominal hysterectomy, bilateral salpingectomy, bilateral gonadectomy, omentectomy and lymph node dissection) was done. Histopathology of the mass revealed mixed germ cell tumor consistent with dysgerminoma, yolk sac tumor and gonadoblastoma. To better differentiate these tumors, immunohistochemistry was performed using Placenta-Like Alkaline Phosphatase (PLAP), Cluster Designation

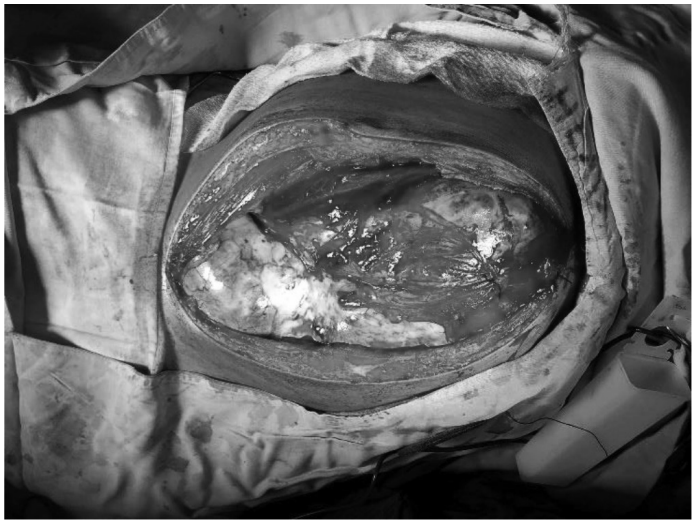

Figure 5. Left ovary was noted to be enlarged to 40 x 26 x 16 cm, solid, multilocular with papillated capsule, irregular borders, thick-walled, with no point of rupture

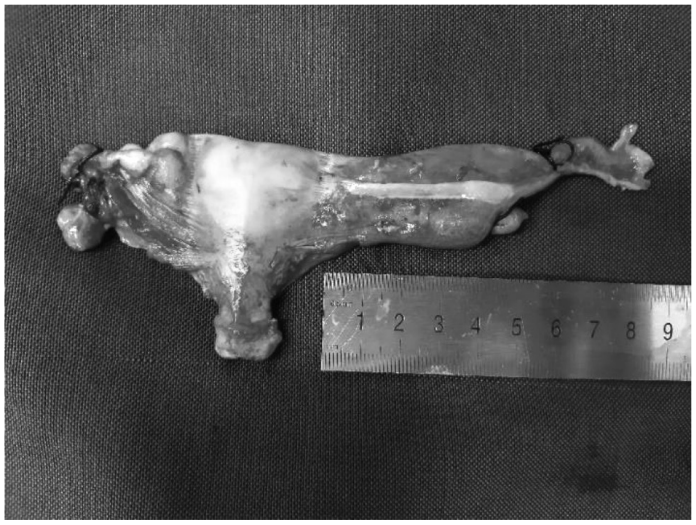

Figure 6. Uterus was small measuring 3x4x1cm, grossly normal with streak gonads

(CD) 17, Alpha Feto-protein, Beta Human Chorionic Gonadotropin (B-hcg), inhibin and cytokeratine. These confirmed the presence of dysgerminoma and yolk sac tumor.

Peritoneal washing was positive for malignant cells. Omentum and lymph nodes were negative for tumor. The patient was discharged on the 10th hospital day with the final diagnosis of Primary amenorrhea secondary to Swyer syndrome with malignant degeneration of the dysgenetic gonad on the left (mixed germ cell tumor: dysgerminoma and yolk sac tumor), FIGO Stage IIB s/p peritoneal fluid cytology, total abdominal hysterectomy, bilateral salpingectomy, bilateral gonadectomy, omentectomy and lymph node dissection. She was advised to come back after a week to finalize plans for chemotherapy and for counseling to address the psychological and emotional concerns brought about by the disordered sexual development. However, she failed to return and efforts to contact her were futile. She has returned to a remote area in Samar where communication by phone is not possible according to her relatives in Manila.

DISCUSSION

Swyer Syndrome [or pure gonadal dysgenesis (PGD)], is a rare disorder of sexual differentiation in males. The exact incidence is not known although reports approximate 1:80,000-100,000.[3] It was first described in 1955. The individual has a 46 XY karyotype but is phenotypically female, and presents with primary amenorrhea. It results from failure of the undifferentiated gonads to develop into testes due to a defect in the SRY gene (or the testes determining gene) on the Y chromosome. Thus, this individual will be genotypically male but appear phenotypically female, with only streak gonads. The gene defect is either sporadic or familial, with X-linked or autosomal recessive patterns of inheritance. Mutations of the SRY gene are seen in 10 -15% of cases.[3]

Until the sixth week of embryonic life, the developing gonad is bipotential. Male sexual differentiation is initiated by the SRY (sex-determining region Y) gene on the Y chromosome, which leads to the development of the gonad into a testis. Sertoli cells secrete anti mullerian hormone to suppress mullerian duct development. Testosterone from the Leydig cells enhances Wollfian duct and male external development.[4] Absence of testicular development leads to absence of AMH (or Mullerian inhibiting susbtance), with subsequent differentiation of mullerian structures (uterus and fallopian tubes) and female external genitalia. Swyer individuals have elevated gonadotropins, normal female androgens, and low estrogens. Streak gonads display fibrous tissue that vaguely resembles ovarian stroma but with no follicles. In females, two X chromosomes are necessary for full ovarian development. Absence of one will lead to formation of streak gonads, as seen in Turner syndrome (45XO).[3]

Because of their female appearance, Swyer individuals are raised as such, only to be discovered otherwise in their teenage years due to primary amenorrhea. Our patient reached 18 years old without menses, and this did not seem to bother her. Her consultation was prompted by the abdominopelvic mass. Individuals with primary amenorrhea warrant investigation when they reach 13 years old without secondary sexual characteristics or 16 years old with well-developed secondary sexual characteristics but

no menarche.[1] This is to ensure that the exact etiology is known and corrected to avoid lifelong consequences like malignancy, infertility, endometriosis, hypertension, diabetes, and psycho-social, sexual and emotional derangement.

Workup of primary amenorrhea involves 1) ruling out a pregnancy, and 2) a systematic evaluation of the hypothalamic-pituitary-ovarian axis and the outflow tract. A pregnancy test in our patient was negative. Serum FSH was elevated, indicating failure of the ovaries to produce enough estrogen and therefore, absence of negative feedback on the hypothalamus and pituitary. Serum prolactin if elevated would lead to hypoestrogenemia but this was not done in our patient because she did not have galactorrhea. Testosterone was in the low levels for females. Ultrasound will assess outflow tract. Our patient's uterus had infantile proportions and the endometrium was markedly thin, suggesting a hypoestrogenic state. What clinched the diagnosis of Swyer syndrome was the chromosomal analysis showing a 46 XY complement.

Our patient had the typical signs of Swyer syndrome: (normal height, underdeveloped breasts, axillary and pubic hair present.) Androgens from the adrenal gland stimulate pubic hair growth and its conversion into estrogen in adipose tissue promotes breast development, as well as the typical female external genitalia. Her uterus is infantile due to lack of sufficient estrogen stimulation. Her gonads are dysgenetic - only a small strip of fibrous tissue, with no hormonal function, so her hormonal assay showed hypergonadotropic hypogonadism.

With gonadal dysgenesis as the most common etiology of primary amenorrhea, a diligent search for the presence of a Y chromosome is necessary because of the increased risk of malignant transformation into gonadoblastoma or dysgerminoma in the streak gonad. Immediate gonadectomy, either laparoscopically or by open abdominal approach, is recommended.[7] Unfortunately, gonadal malignancy was already present in our patient. She missed that window of opportunity to have her gonads removed immediately, which would have prevented the malignancy.

Mixed germ cell tumors account for 10-20% of all malignant germ cell tumors of the ovary. In our patient, dysgerminoma and yolk sac tumor (endodermal sinus tumor) coexisted within the same tumor. It is reported to be the most common combination although immature teratoma, embryonal carcinoma and choriocarcinoma are seen occasionally. The elevated alpha feto-protein in our patient is due to the yolk sac tumor component. Because of financial constraints, a full panel of tumor markers for germ cell tumors which should also include human chorionic gonadotropin (HCG) and Lactic dehydrogenase (LDH) were not requested. Because of the dysgerminoma, an elevation of LDH would have been seen.

The management of mixed germ cell tumors should be tailored according to the most aggressive tumor element. Dysgerminomas contain germ cells that have not differentiated into embryonic or extraembryonic structures. Although considered to be malignant and rapidly growing, they are often not aggressive and are highly sensitive to adjuvant chemotherapy particularly with bleomycin, etoposide and cisplatin given for three to four cycles[10]. Radiotherapy is reserved for those who cannot undergo chemotherapy because of the long term toxicities associated with radiation. The mean 5-year survival rates of this tumor among gonadal dysgenesis compared with normal individuals are similar and are dependent on tumor stage, with 96% in early stage and 54% in advanced stages.[3] Yolk sac tumors originate from germ cells that differentiate into the extraembryonal yolk sac. Although reported in the 1990s to have a very poor prognosis, with 80-90% of patients dying within 2 years of diagnosis, yolk sac tumors have now been found to have a very good response especially in young patients, following surgery and chemotherapy using the same agents for dysgerminoma. The 5-year median survival rate for early stage is 94%, and 90% for advanced disease.[5] Therefore, for our patient, treatment with bleomycin, etoposide and cisplatin for 3 to 4 cycles, followed by monitoring of tumor markers LDH and AFP to detect recurrence would be the optimum plan.

Patients with dysgerminoma and yolk sac tumor are good candidates for fertility preserving surgery because of their good response after chemotherapy, even with advanced stage disease.[10] Rates of relapse after radical surgery compared with conservative surgery for the ovaries and the uterus were not different. In our patient, it was necessary to remove the dysgenetic gonads but preservation of the uterus would have been an option. Our patient is young and if future fertility was considered, given that the tumor response to surgery and chemotherapy is good, uterine preservation should have been considered. This would only be possible if this was planned preoperatively to secure an informed consent which includes the benefits and potential risks of preservation, and to schedule a frozen section to determine the tumor type and its behavior before deciding intraoperatively on a conservative procedure. Successful pregnancies in Swyer syndrome have been reported since 1988.[8] But because our patient's uterus was removed, ART with oocyte donation and embryo transfer is not anymore possible. Uterine transplantation is still in its experimental stage. Adoption is also an

option.

Disclosure of the true gender is a controversial and delicate issue that should involve not just the patient but her family as well. Counseling is a cornerstone of therapy, averting depression and suicidal thoughts and enhancing satisfactory sexual functioning in adulthood. Our patient has been raised as a female but seems to be attracted to females. Should she decide to remain a female, estrogen therapy may help enhance her secondary sexual characteristics and increase bone mass. In patients with uteri, estrogen-progesterone therapy may induce withdrawal bleeds that may give some semblance of menstruation. Should her sexual preference be male, androgen therapy may be instituted.

SUMMARY

A case of an 18-year-old with Swyer syndrome and malignant degeneration of her dysgenetic gonads was discussed. This report calls attention to the need for timely and thorough investigation of primary amenorrhea to identify individuals with a Y chromosome who will require timely prophylactic gonadectomy to avert degeneration of these gonads into malignancy. An accurate and prompt diagnosis, using a systematic approach to the amenorrhea work-up will facilitate diagnosis and performance of gonadectomy before malignancy sets in. This will ensure preservation of fertility, reduction of psychosexual and emotional trauma, and improvement in patient survival. ■

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