The XY Female: A Rare Case of Swyer Sydrome with Dysgerminoma

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Swyer Syndrome is a pure form of gonadal dysgenesis that although rare, should not be disregarded in the differential diagnosis of patients who present with primary amenorrhea and abdominopelvic mass. The dysgenetic gonads fail to produce antimullerian hormone in an individual with Swyer Syndrome who is genetically male, resulting in feminization and absence of virilization. Phenotypically female, they usually seek consult at a later time during their teenage years due to primary amenorrhea. Our index patient consulted due to a large abdominopelvic mass and primary amenorrhea. Hormonal assay showed a hypergonadotropic hypogonadism endocrinologic milieu, and on karyotyping, showed a genetically male individual. This paper shall discuss an in-depth pre-operative, surgical and post-operative management of patients diagnosed with Swyer Syndrome.

Key words: Swyer syndrome, dysgerminoma

Introduction

A rare entity diagnosed during late adolescence, Swyer Syndrome is a pure form of gonadal dysgenesis with a 46 XY karyotype. Patients consult due to lack of menses after the expected time of puberty. They have the normal female external genitalia, with hypoplastic breasts and uterus. Early diagnosis is very important because of the increased risk in development of gonadal tumors, up to 30%, with 10-20% preponderance for bilaterality.[1,2,3,4]

Dysgerminoma accounts for less than 1% of ovarian neoplasms.[5] It is the second most common tumor seen among patients with Swyer Syndrome, next to gonadoblastoma. Surgical management is the standard treatment and can achieve a cure rate of as high as 95% when tumors are completely resected.[1,5] Fertility-preserving surgery is also acceptable in these patients, with good survival outcomes. In patients with Swyer Syndrome and dysgerminoma, counselling prior to operative procedures is important to ensure adequate follow up and good prognosis.

Discussed in this paper is a case of Swyer Syndrome presenting with a large abdominopelvic mass and amenorrhea.

The Case

The patient is JL, a 16-year old adolescent who consulted at the gynecology clinic due to a hypogastric mass. She had no known co-morbidities and had an unremarkable past medical, surgical and family history. JL is the youngest of five siblings, born to a then 32 - year old mother. The patient stopped going to school at the age of twelve due to financial constraints but her developmental milestones were at par with her age. She had no vices. Patient never had coitus.

Her history started two months prior to consult when she noted an abdominal mass noted at the level of the umbilicus. She was also noted to have

primary amenorrhea, and a 20% weight loss in a span of 2 months. She had no fever, headache, blurring of vision, nor changes in the urinary and bowel movement.

JL weighed 36 kilos with a height of 153 cm. She had stable vital signs and unremarkable head, neck, chest and heart findings. A non-tender, mobile and predominantly solid mass was palpated at the abdomen, from the suprapubic area up to two centimeters above the umbilicus, measuring approximately 16cm x 16cm. She had full and equal pulses, pale nailbeds, with no cyanosis or edema.

Pelvic examination showed normal female external genitalia, with sparse pubic hair (tanner stage 2). She had smooth nulliparous vagina, five centimeters long, a smooth, firm cervix,and small uterine corpus. Breast development was tanner stage 2.

A transrectal and transabdominal sonologic examination revealed the following: The uterus is retroverted with smooth contour and homogeneous echopattern measuring 3.6cm x 1.8cm x 1.4cm (Figure 3). The cervix measures 1.4cm x 1.2cm x 1.2cm, with homogeneous stroma and distinct endocervical canal. The endometrium is linear measuring 0.2 cm, with intact subendometrial halo. Both ovaries are not visualized. Occupying the abdominopelvic cavity is an irregular, solid, movable mass measuring 15.5cm x 13.5cm x 12.2cm. There is no free fluid in the abdominopelvic cavity. Color flow mapping of the abdominopelvic mass shows moderate vascularity which on Doppler interrogation revealed low resistance indices (PI=0.43, RI=0.38) (Figure 4). Sonographic impression: Abdominopelvic mass, consider ovarian new growth, probably malignant by Sassone = 12,

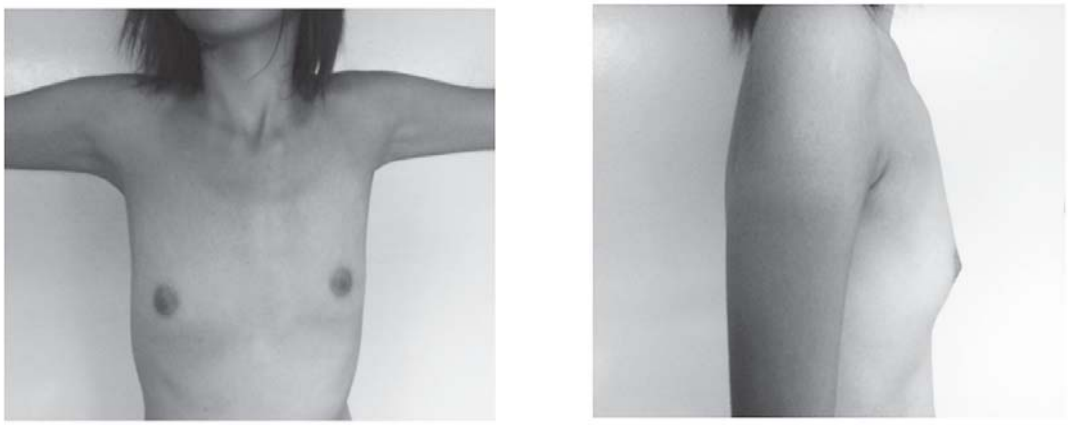

Figure 1. Tanner stage of JL. Notice that her breast is only at tanner stage II.

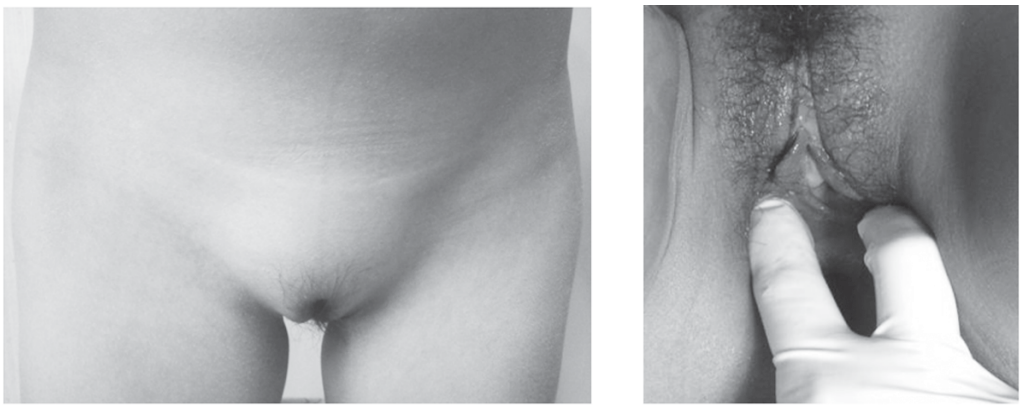

Figure 2. External genitalia of JL. She had normal female external genitalia. Her pubic hair, at age 16, is at tanner stage II, as well

Lerner = 7, IOTA = Solid, color score of 3; Small uterus for age.

Assessment during this time was primary amenorrhea, ovarian new growth, probably malignant. Serum FSH, estradiol, CA 125, AFP and LDH were requested. Patient and relatives were counseled that an operative procedure is needed. She was referred to the Pediatric Adolescent Service for pre-operative clearance.

Serum FSH was elevated at 172 uIU/mL (normal range at 5-10 uIU/mL), and serum estradiol was low, at 1.7 pg/mL (normal range at 20 – 534 pg/mL), depicting a hypergonadotropic hypogonadism milieu. Tumor markers done were as follows: CA 125 8.89 U/mL (normal values at 0-35 U/mL), AFP 0.05 ng/mL (normal range 0-5 ng/mL) and LDH 2118 IU/L (normal values at 266-500 IU/L). Karyotyping showed a 46,XY complement. With these results, the working impression at that time was Swyer Syndrome, and Ovarian new growth, probably Dysgerminoma.

JL was then referred to the Endocrinology and Genetics service for co-management. During OPD follow up, counseling was done. Patient and relatives were presented with options and the corresponding consequences. One option was to do bilateral gonadectomy with complete staging, leaving the uterus behind, and the other is to do bilateral gonadectomy, total hysterectomy, with complete surgical staging. Normally, conservative

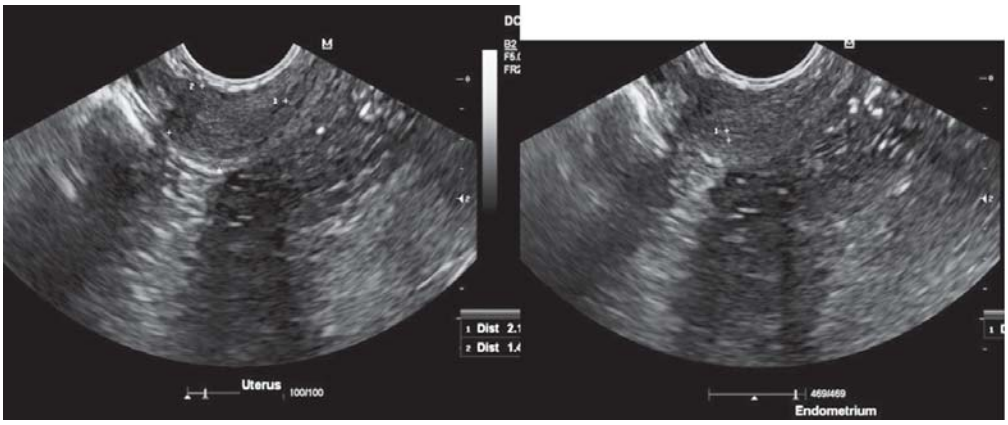

Figure 3.Transrectal and transabdominall ultrasound: The uterus and endometrium. The uterus is retroverted with smooth contour and homogeneous echopattern measuring 3.6cm x 1.8cm x 1.4cm. The endometrium is linear measuring 0.2 cm, with intact subendometrial halo.

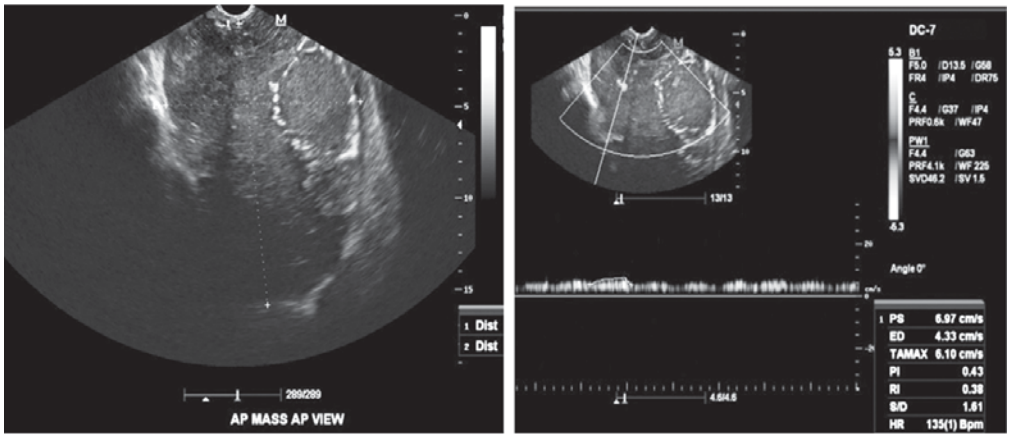

Figure 4. Abdominopelvic mass and Color Flow mapping of the mass. Occupying the abdominopelvic cavity is an irregular, solid movable mass measuring 15.5cm x 13.5cm x 12.2cm. Color flow mapping of the abdominopelvic mass shows moderate vascularity which on Doppler interrogation revealed low resistance indices (PI=0.43, RI=0.38).

management for future fertility in a young female with dysgerminoma is recommended, as cure rates are very high in these patients, especially when the tumor is captured at an early stage.

JL and her relatives were given time to think about the options. On follow up, their decision was to undergo bilateral gonadectomy, with frozen section, and if the result shows a benign tumor, the uterus is left behind. But if frozen section shows a malignant tumor, then a total hysterectomy with complete surgical staging shall be performed.

Preoperatively, patient was referred to the Gynecology Oncology service for possible surgical staging. Because her hemoglobin was low (86 g/dl), she was transfused with 2 units pRBC preoperatively. After correction of the anemia, patient underwent exploratory laparotomy, peritoneal fluid cytology, bilateral gonadectomy, with frozen section. Once the frozen section revealed dysgerminoma, the surgeons proceeded with total hysterectomy, infracolic omentectomy, random peritoneal biopsy, bilateral lymph node dissection, and paraaortic lymph node sampling. Intraoperatively, there was no ascites. The liver, subdiaphragmatic surface, gallbladder, spleen, kidneys, intestines, omentum and appendix were smooth and grossly normal. There were no palpable pelvic and paraaortic lymph nodes. The right ovary is converted to a solid mass measuring 17.0cm x 14.5cm x 9.5cm, which on cut section showed smooth pale brown surface, with lobulated areas and central collagenous scar. The uterus measured 5.0cm x 3.0cm x 1.0cm, with smooth, tan serosal surface. (Figure 5) On cut section, the cream-white myometrium measured 0.8 centimeter. The endometrium measured 0.2 centimeter, smooth, tan-white in appearance. The uterine canal measured 4.5 centimeters deep, 2.0 centimeters of which is the endocervical canal. The cervix measured 2.0cm x 1.0cm x 1.0cm, grossly normal. The left gonad measured 1.0cm x 0.5cm x 0.5cm, with note of central whitish fibrous area.(Figures 6 & 12) The left fallopian tube measured 7.0cm x 0.3cm x 0.3cm. Both fallopian tubes were grossly normal.

Post-operatively, patient was referred to Child Psychiatry for counseling. She had a relatively unremarkable post-operative course and went home on her fourth post-operative day.

Histopathologic result revealed: Dysgerminoma, right ovary, No definite lymphovascular invasion seen; Negative for tumor: all 3 lymph nodes in specimen labeled "R external iliac LN", all 2 lymph nodes in specimen labeled "L external iliac LN", all 3 lymph nodes in specimen labeled "R obturator LN", 1 lymph node in specimen labeled "L obturator LN", 1 lymph node in specimen labeled "aortic LN", fibrocollagenous tissues in specimens labeled "R pelvic side wall", "L pelvic sidewall", "R

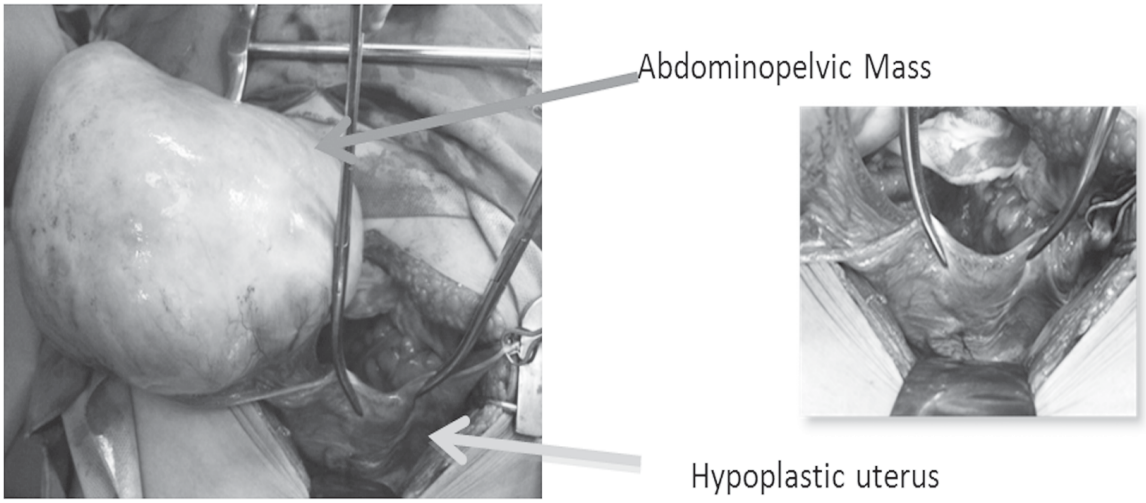

Figure 5. Intraoperative findings: Anterior view of the mass (left side) and uterus (right portion, closer view).

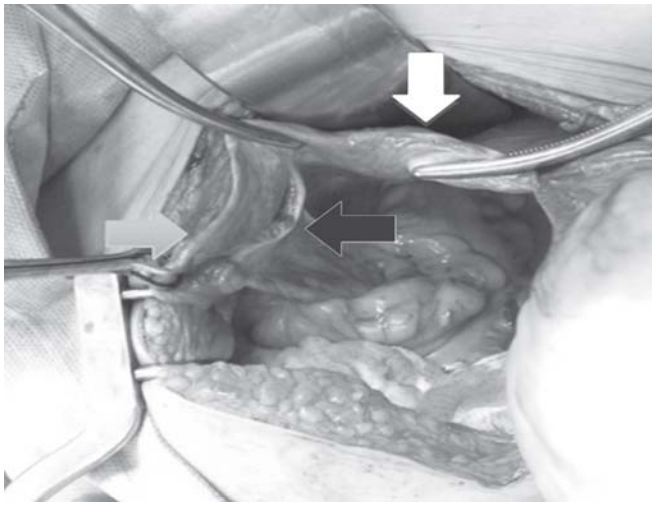

Figure 6. Intraoperative findings: Posterior view of the uterus (white arrow) showing the left gonad (black arrow) as a longitudinal streak below the fallopian tube (gray arrow).

Figure 7. Microscopic view of right gonad. There is proliferation of epithelioid cells admixed with mature lymphocytes arranged in sheets or small clusters separated by thin, fibrous septae (gray arrow).

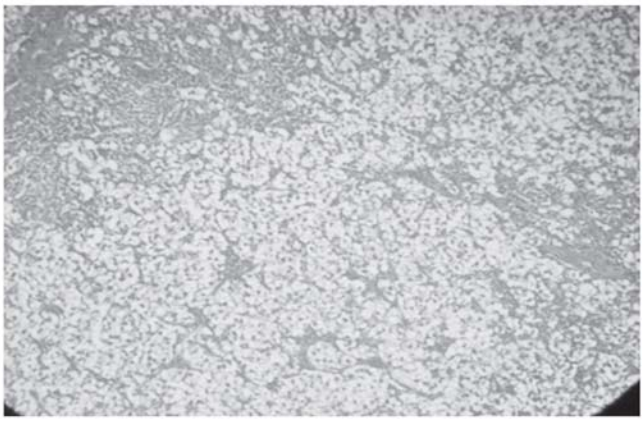

Figure 8. High power view of right gonad. The cells have clear cytoplasm with distinguishable borders and large nuclues.

Figure 9. Left gonad. The left arrow points to fibrous tissue. The white arrow points to an area of the gonad with streaks of normal ovarian tissue.

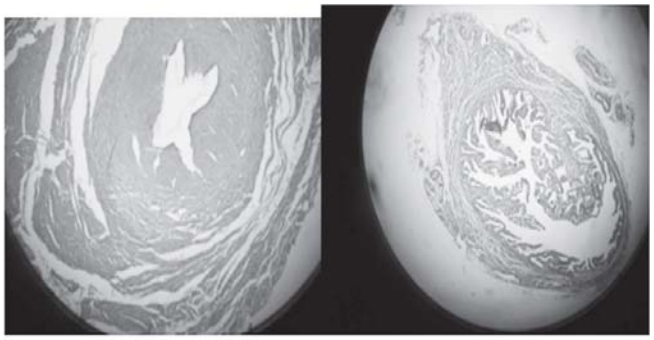

Figure 10. Fallopian of the left (left portion) and right gonad (right potion).

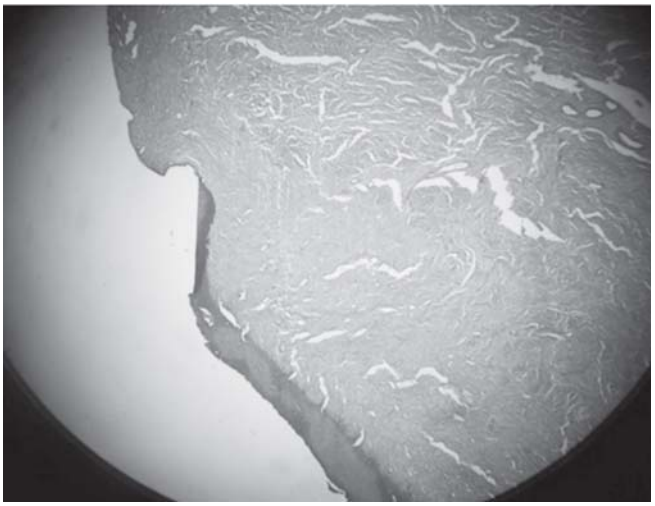

Figure 11. Squamocolumnar junction of the cervix. Notice the multilaminar epithelium of the ectocervix at the lower portion and the unilamilar columar epithelium of the endocervix.

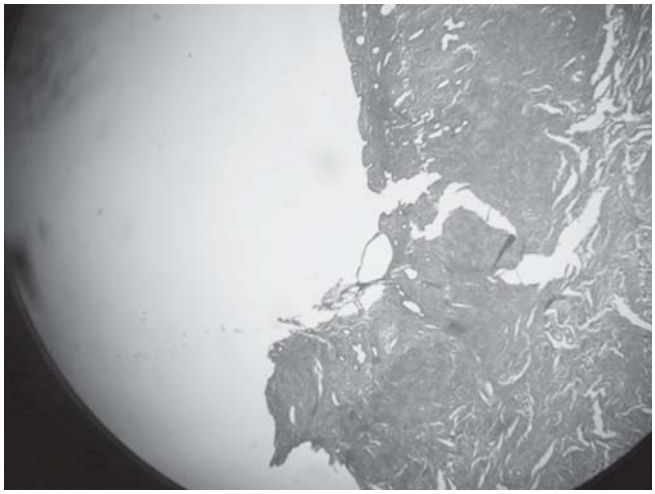

Figure 12. Low power magnification of the endometrium and myometrium of the uterus. The endometrium looks atrophic, with tubular glands.

paracolic", "L paracolic", "cul de sac" and "bladder", specimens labeled "omentum" and "peritoneal cavity". Basal endometrium; Chronic cervicitis with nabothian cyst; One small focus of ovarian stroma, specimen labeled as "gonadal streak". No diagnostic abnormality recognized: bilateral fallopian tube.

Discussion

First described by Jim Swyer in 1955, Swyer Syndrome is a form of pure gonadal dysgenesis with an incidence of 1:80,000-100,000.[1,2,3,4,6] The patients usually do not consult until during their late adolescent period due to amenorrhea. Raised as females, they are usually referred to the gynecologists for management. JL, already 16 years old, consulted at our gynecologic clinic due to a palpable hypogastric mass and primary amenorrhea. Feminization and absence of virilization is due to the dysgenetic gonads that failed to produce the antimullerian hormone. [7] The dysgenetic gonads resulted from a sporadic mutation either in the YP11 location of SRY (sex determining region of Y chromosome) or in other genes that affect testicular differentiation, such as SOX9, DAX1, WT1 or SF1.[6] Production of antimullerian hormone is thereby inhibited which leads to the development of the female genital tract during embryonic stage.[6,7]

Differential diagnosis include Androgen Insensitivity Syndrome (AIS) and mixed gonadal dysgenesis. Patients with AIS, like Swyer Syndrome, have 46 XY karyotype, are phenotypically female, with normal female external genitalia and present with amenorrhea. Unlike Swyer, physical examination of patients with AIS would reveal a well-developed breast. On pelvic examination, the vagina ends in a blind pouch and no uterus can be palpated, which can be confirmed on imaging.[8] Its incidence is higher than Swyer syndrome, at 1:40,000.[7] In phenotypically female patients with mixed gonadal dysgenesis, their clinical presentation can be the same as patients with Swyer Syndrome, with normal female external genitalia, hypoplastic breasts and uterus but on histopathologic examination, the gonads exhibit testicular differentiation in addition to ovarian differentiation. Karyotyping would also show mosaicism (46 XX, 46XY). [6]

Patients with Sywer Syndrome frequently consult due to amenorrhea. They present in their adolescent stage with delayed pubertal maturation. Hormonal assays show a hypergonadotropic hypogonadism milieu. They have elevated FSH and LH levels. Estrogen is expectedly low, hence minimal breast enlargement is larghely due to peripheral aromatization of androgens.[4] However, in those patients who do menstruate, ovarian tumor should be suspected.[9]

In general, patients with gonadal dysgenesis have a 20-30% risk of developing germ cell tumor.[1,2,3,6] The risk is higher in Swyer Syndrome, which is as high as 40%.[8] Gonadoblastoma is the most common germ cell tumor followed by dysgerminoma.[2,3,9,10] It is therefore recommended that once diagnosis of Swyer Syndrome is established, bilateral gonadectomy should be performed after development of secondary sexual characteristics. Patients are started on hormonal replacement therapy thereafter.

Dysgerminomas are malignant germ cell tumors that affects women of reproductive age. It is more common in patients with gonadal dysgenesis, hence in patients with high index of suspicion (amenorrhea with abdominopelvic mass), karyotyping should be done. Most useful tumor marker would be LDH, as serum AFP and CA-125

are within normal range in these patients.[11] Around 73% are diagnosed at stage I, 4% at stage II, 21% at at stage III, and less than 5% are diagnosed at stage IV at the time of presentation.[5] When caught at an early stage, surgical management involving fertility-sparing procedures can be performed. [4,5,9,10]

JL presented with abdominoplevic mass and amenorrhea. She was phenotypically female, with normal stature, underdeveloped breasts, enlarged abdomen, normal external genitalia and small uterus for age. Tumor markers showed normal values for CA-125 and AFP, but elevated LDH levels. Because of financial constraints, serum βHCG was not done. Hormonal assays showed elevated FSH, normal TSH and prolactin, and low estradiol levels. Karyotyping was requested due to suspicion of a possible gonadal dysgenesis, which revealed 46 XY, thereby clinching the diagnosis.

Patient was advised constant follow-up for counselling and formulation of a surgical plan. Had this been just a simple case of dysgerminoma, any gynecologist would do a fertility-sparing procedure, by doing just unilateral salpingooophorectomy, with lymph node dissection. However, for a diagnosis of Swyer Syndrome, several issues need to be addressed: first, patient is genetically male. Since patient was raised as female, this disclosure resulted in the patient's gender identity crisis. Relatives were advised to treat her just like they usually did, and continue rearing her as female. Psychiatric counselling was offered to help the patient and to guide the relatives on how to handle such case. This becomes more difficult when patients with Swyer Syndrome are in their adolescent stage. Patients with disorders of sexual differentiation are found to have sexual aversion and low libido. Some avoid intimate relationships as they are afraid of rejection once their partner finds out their condition. Clinicians should build trust with their patients and talk confidentially to patients during their follow-up to encourage them to freely share their thoughts and concerns. Physicians must also be aware that repeated examination and medical photography could be extremely embarrassing for the patient.[12]

The next issue that needs to be addressed is the surgical plan for the patient. Considering her age, fertility-sparing procedure can be offered. Females with dysgerminoma who underwent fertility-sparing surgery were noted to have good outcomes in terms of survival and reproduction, despite administration of chemotherapy. Menstrual function returned in 85% of the patients and 80% of patients who attempted pregnancy was successful. However, will fertility-sparing surgery be beneficial for our index patient? For this case, the actual dilemma is whether to do conservative surgery or do total hysterectomy. There are case reports of patients who became pregnant through oocyte donation and embryo transfer,[1,3,9] although these patients have smaller uterus compared to their normal female counterparts. If we opted to spare the uterus for future reproduction, this would present another serious moral and ethical issue: oocyte donation. The Philippines being a largely Catholic nation, and the index family being members of the Catholic Church, oocyte donation and surrogacy are scientifc advances still considered as taboo. Moreover, the family's meager financial status precludes them from affording such expensive ART procedures, as they already had difficulty procuring funds for the surgery alone. Armed with the knowledge that complete surgical staging confers a high cure rate, the patient and her family consented to the proposed surgical procedure.

Lastly, hormonal replacement therapy will be needed post-operatively and should be started as early as possible. Estrogen therapy must be given at the appropriate time, no later than 15 years old (to prevent bone loss and promote timely development of secondary sexual characteristics) but not before 12 years to prevent early closure of the epiphysis which results to small stature. It is started at a low dose and adjusted gradually according to response every 3-6 months. Sexual maturation should be completed at 2-3 years. In patients still with intact uterus, progestin therapy is added after 12-24 months of estrogen therapy or when vaginal bleeding occurs, whichever happens earlier. The progestin component prevents abnormal uterine bleeding and protects the endometrium from the harmful effects of

unopposed estrogen.[1,3,4,6,10] Our index patient has just started estrogen therapy. Progestin therapy will be unnecessary for her.

Conclusion

Sywer Syndrome is a pure gonadal dysgenesis with a 46 XY karyotype, with an incidence of 1:80,000 – 100,000.[1,4,6] Patients present late in their adolescent life due to delayed sexual maturity and amenorrhea. They have hypoplastic breasts and uterus. Hormonal assay points to hypergonadotrophic hypogonadism. Germ cell tumors of the gonads develop in up to 40% of patients, and the most common would be gonadoblastoma and dygerminoma.[8] Our index patient who consulted for abdominopelvic mass and amenorrhea had these characteristics, arising suspicion of a possible case of gonadal dysgenesis. Karyotyping made the diagnosis definitive.

Management of patients with Swyer Syndrome is aimed at the following: (a) induction of puberty, (b) prevent or stop bone loss (c) fertility preservation, and (d) gonadectomy after development of secondary sexual characteristics.[1,2,3,4,6,10,12,13] Patients should be referred to and managed by a multidisciplinary team. Support groups are encouraged to prevent patients from feeling depressed and alienated from other people. At present, JL is currently on regular follow-up with Reproductive Endocrinology service, the Gynecology Oncology, Pediatric Adolescent, Endocrinology, Genetics, and Child Psychiatry.

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