Gonadoblastoma in a Swyer Syndrome: A Case Report

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Swyer syndrome is a form of complete gonadal dysgenesis, characterized by a 46, XY karyotype with female phenotype. They present with primary amenorrhea and absence of secondary sexual characteristics. It is believed to be due to SRY gene deletions or mutations. They are born with female external genitalia and not suspected until puberty fails to occur. This paper presents a case of 22-year old female with female external genitalia, an infantile uterus and cervix and streak gonads and absent secondary sexual characteristics, who presented with primary amenorrhea. Gonadotropin levels are elevated with low estradiol levels. Karyotype showed a normal male 46,XY. Since the streak gonads have the propensity for tumor development in 20-30% of the cases, laparoscopic bilateral gonadectomy with salpingectomy was done which showed gonadoblastoma on the right gonad. Early diagnosis is crucial in the initiation of treatment to prevent osteoporosis and enhance development of secondary sexual characteristics and eventually initiation of menstruation. In-vitro fertilization using donor oocyte has proven to be successful in some reported cases.

Key words: Swyer syndrome; 46,XY Complete Gonadal Dysgenesis; Hypergonadotropic hypogonadism; Primary amenorrhea; SRY gene mutation; Streak gonads

Introduction

The gender identity of a person is determined by their genetic, gonadal, and phenotypic sex and also is influenced by their environment. Genetic or chromosomal sex is defined by the sex chromosomes, typically XX or XY. Gonadal sex is defined by the direction of gonadal differentiation, into ovaries or testes. Phenotypic sex is defined primarily by the appearance of the external genitalia and the secondary sexual characteristics that develop at puberty. Sexual expression, both homosexual and heterosexual, reflects the sum of all sexual influences on the individual, both prenatal and postnatal, the latter referring to the role assigned by society in accordance with the individual's phenotype and behavior. The processes involved in sexual differentiation of the embryonic brain are less clear, but may involve mechanisms similar to those controlling differentiation of the external genitalia.[1]

Normal sexual differentiation begins with genetic or chromosomal sex, as established at the time of fertilization.[1] Normal gonadal development required normal germ cells and normal gonadal somatic cells.[2] Gonadal development begins during the fifth week and persists until 9 weeks of gestation. At this stage of development, the gonads are identical in males and females, indifferent and bipotential, capable of differentiating into either testes or ovaries in response to inductive signals.[3] Many genes, such as *SF1, LIM1, EMX2 and LHX9*, act in early establishment of gonads in both male and female

(Figure 1). The initiation of this development depends on the activation and interaction of several genes, such as *DHH, FGF9, M33, DMRT1, AMH, SRY and SOX9*. *SOX9* is a major candidate for the testis- inducing gene, and *SRY* is believed to be the sex-determining factor (SDF) of males. *SOX9* and *SRY* are located on the short arm of the Y chromosome. *SRY* activation of *AMH* leads to the degeneration of the mullerian ducts and thus the generation of a male. In the absence of AMH, the mullerian ducts develop into the upper vagina, cervix, uterus and oviducts thereby generating normal female internal genitalia. Potential candidates for the SDF in females are *RSPO1, DAX1* and *WNT4.*[4] External or internal factors that modify the normal developmental processes can lead to chromosomal or gonadal abnormalities that may or may not be apparent at birth.

Disorders of sexual development (DSD), previously known as intersex disorders, are congenital conditions characterized by atypical development of chromosomal, gonadal or phenotypic sex. Traditionally, they have been classified according to gonadal sex (True hermaphrodite, male and female pseudohermaphrodite). The new classification and nomenclature of DSD.[5] is now being used and this was organized by chromosomal composition and causation. The term gonadal dysgenesis refers to a variety of diseases in which the development of the indifferent embryonic gonads to differentiated gonads is inhibited. Disorders of testicular development include complete gonadal dysgenesis (46,XY), partial gonadal dysgenesis (46,XX) and the loss of otherwise normally developed testes during fetal life. 46,XY gonadal dysgenesis results

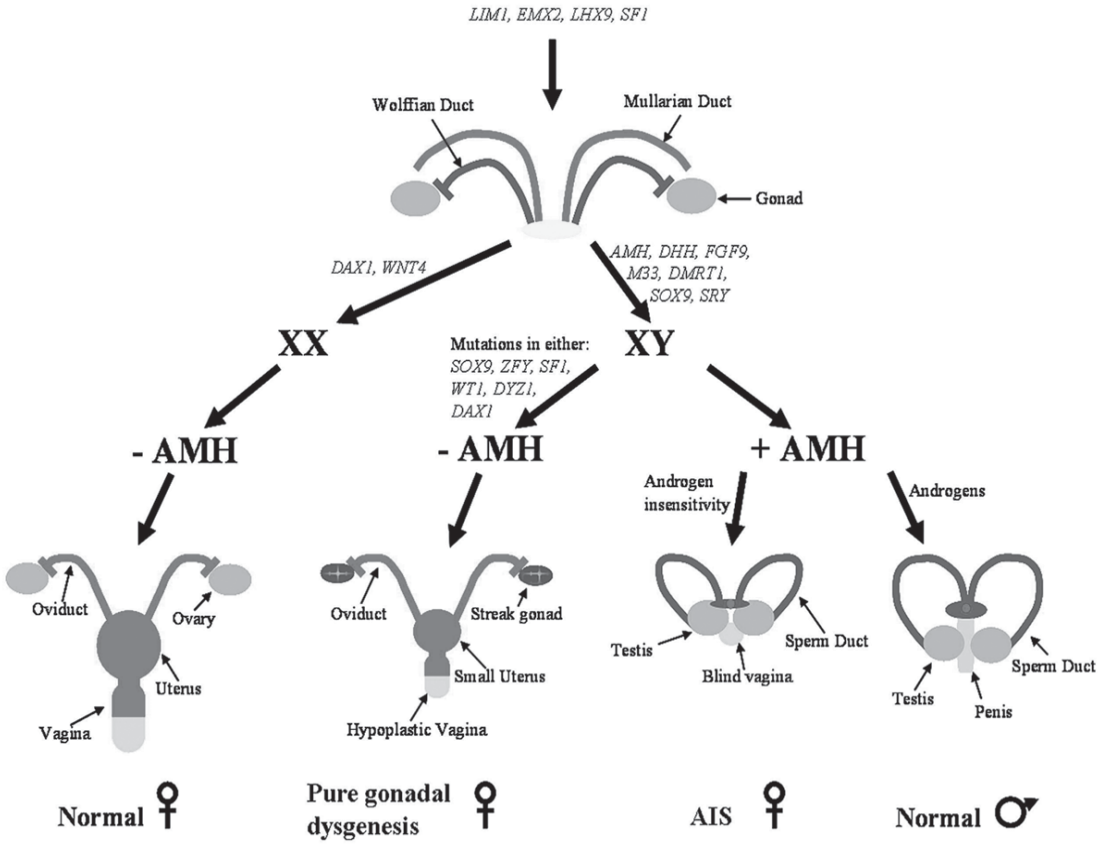

Figure 1. Embryologic development of sex organs in normal females, males, and patients with AIS and pure gonadal dysgenesis. Significant genes are shown for each step of the process. Presence or absence of AMH is shown by plus or minus signs, respectively. (Adapted from Jorgensen. Care of XY women: a clinical practice guideline. Fertil Steril 2010)[4]

from deletions or point mutations in the *SRY* gene. Mutations in *SRY* were found in less than 20% of the patients with complete 46,XY gonadal dysgenesis. To date, more than 53 mutations have been identified within the *SRY*, and most of them (43 mutations), are located in the HMG box.[6]

G.J. Swyer first described two cases of sex reversal that differed from the known forms of what was then termed 'male pseudohermaphroditism'.[7] From then on, it was then coined as Swyer's Syndrome or 46, XY Complete Gonadal Dysgenesis (CGD) in the new classification. The exact incidence is unknown but can be estimated at 1:80,000 births.[8] A study of 326 patients with primary amenorrhea showed that 3.4 % were XY females.[9]

Many of the patients are first diagnosed at puberty, when they present with absence of menarche. They seek medical attention for the evaluation of primary amenorrhea and possible lower abdominal pain or mass. Early diagnosis in childhood is only possible if a karyotype is carried out for other reasons, such as for example as part of prenatal diagnosis of aneuploidy or as part of familial screening following the diagnosis of a sibling with the condition.

There are three reported cases of Swyer's syndrome in the Philippines.[10,11,12] One case presented with primary infertility who initially was treated for primary amenorrhea at 23 years old. Two of the local cases presented with an abdominal mass, which showed dysgerminoma and endodermal sinus tumor. All had a 46,XY karyotype with normal female external and internal genitalia and streak gonads.

Complete gonadal dysgenesis (CGD) or Swyer syndrome is characterized by bilateral streak gonads, normally developed Mullerian ducts, female external genitalia, and hypergonadotropic hypogonadism, that is, elevated gonadotropin and decreased estradiol (E2) levels.[13] Such individuals usually present with primary amenorrhea and absence of secondary sexual characteristics. Majority of them are thin with a normal or tall stature, because of a height gene present on the Y chromosome.[14,15]

A high incidence of gonadoblastoma and germ cell malignancies has been reported and estimated to be between 15 to 35%[5], and therefore, the current practice is to proceed to gonadectomy once the diagnosis is made.[16] Dysgerminoma is the most common malignant germ cell tumor of the ovary. It can be found either in a pure form or mixed with other germinal elements. Therefore in premenarchal patients with a pelvic mass, the karyotype should be determined. About 65% of dysgerminomas are stage I at diagnosis. About 85 to 90% of stage I tumors are confined to one ovary; 10–15% is bilateral. Dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality, other germ cell tumors being rarely bilateral.[17] The treatment of patient with early dysgerminoma is resection of the primary lesion and proper surgical staging. The most frequently used chemotherapeutic regimen for germ cell tumors in BEP (Bleomycin, Etoposide, Cisplatin). Cases of successful pregnancies have been reported.[8,18,24] Pregnancies were possible through oocyte donation and hormonal treatment and in-vitro fertilization.

The Case

This is a case of a 22-year old phenotypically female, single, and the eldest of two siblings. The sisters were born and raised in Samar and later migrated to Bulacan. She had grossly normal female-looking external genitalia at birth. Childhood history was unremarkable. There were no problems encountered during her elementary and high school days. There was no report of neurodevelopmental delay. Her younger sister had her menarche before the patient even had one, and is currently married with 2 children. Family history was unremarkable. She presently works as a house help.

During her growing up years, gender identity never became a problem for the patient. She was raised as a female. She had 1 sexual partner and her first sexual contact was at age 21 and claims no dyspareunia.

She consulted our clinic due to primary amenorrhea. There was no complaint of cyclic pelvic pain, vasomotor symptoms, and headache or mood changes. There was also no history of accidents resulting to fractures.

On physical examination, patient is phenotypically female patient (Figure 2), with lean body mass and a height of 5 ft. and 8 inches (172 cm) and a weight of 54 kg (BMI of 18.1). Skin was not dry and no hirsutism was noted. Breast and pubic hair development were both Tanner stage II (Figure 3A and 3B). There were no midline hair or abdominal masses palpated. The external genitalia was grossly female but with flattened labia majora (Figure 4). The clitoris was not enlarged. Speculum examination showed a small, smooth and short cervix measuring 1cm x 1.5cm (Figure 5). The vaginal canal was not shortened. On bimanual examination, the vagina admits 2 fingers snuggly; the cervix was closed; the body of the uterus was non-palpable, as well as the adnexa; there were no rectovaginal nodulations palpated.

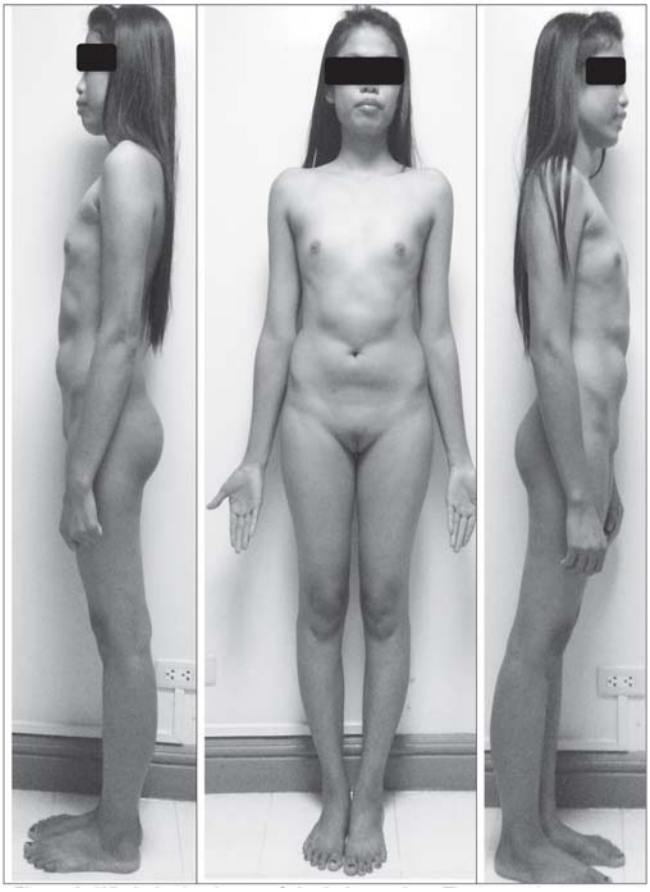

Figure 2. Whole body picture of the index patient. The external appearance or phenotype is female. This shows the lean body mass of the patient devoid of fatty tissue. She is 5 ft and 8 in tall.

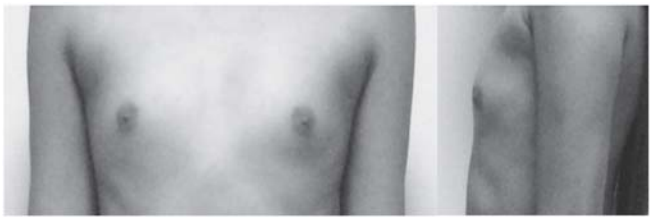

Figure 3A. Breast development of the index patient. There was breast bud with slight elevation of the breast representing a Tanner Stage II (Picture taken after 6 cycles of HRT).

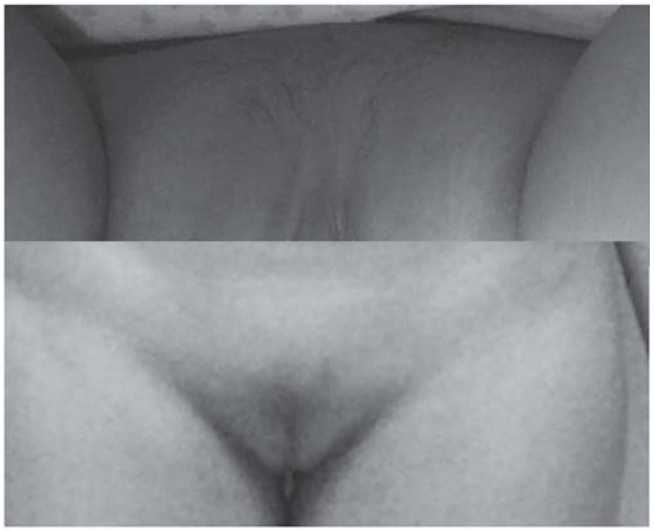

Figure 3B. Tanner Stage II Pubic hair development. The mons pubis was devoid of fat pad with sparse, short and pigmented pubic hair along the midline.

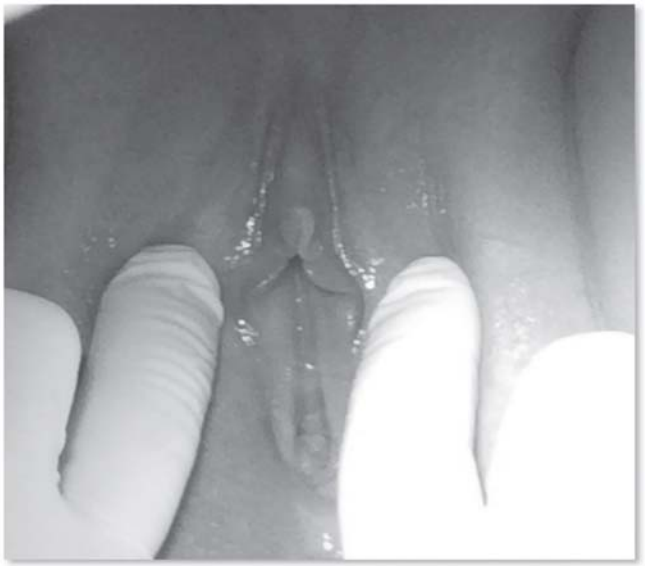

Figure 4. External Genitalia of the index patient. This shows a female external genitalia. The labia majora was flattened with small labia minora. On further inspection, the hymen was partially intact and no clitoris was identified. There was no septum or masses noted.

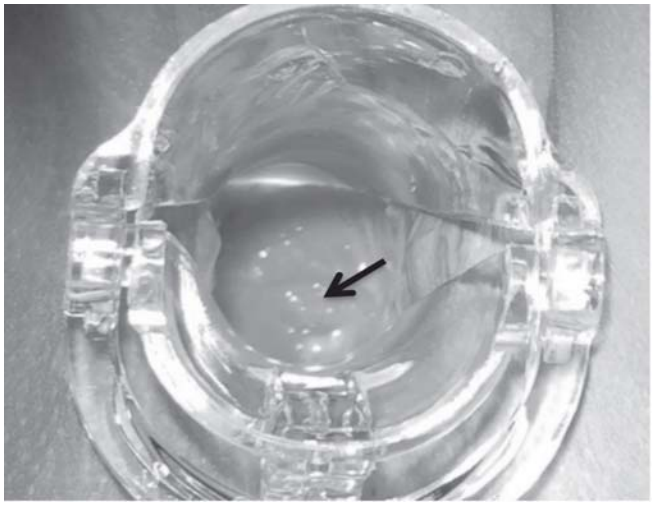

Figure 5. Speculum exam. The vaginal canal measured 7 cms in length. The fornices were formed. The cervix (with arrow) was small measuring 1cm x 1.5cm. The cervical os is closed. Vaginal walls were smooth.

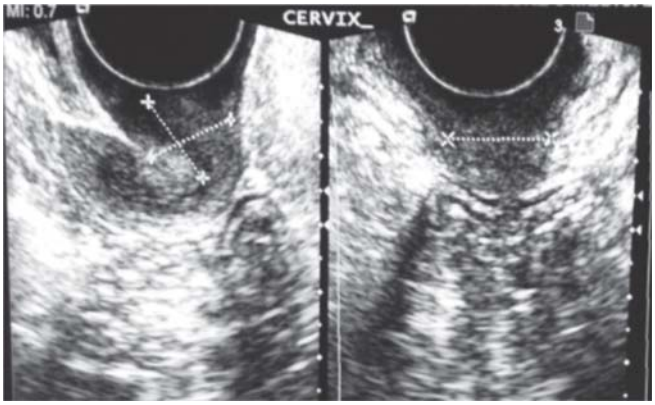

Figure 6A. Transvaginal ultrasound showing measurement of the cervix. The cervix measured 1.3cm x 1.5cm x 1.3cm.

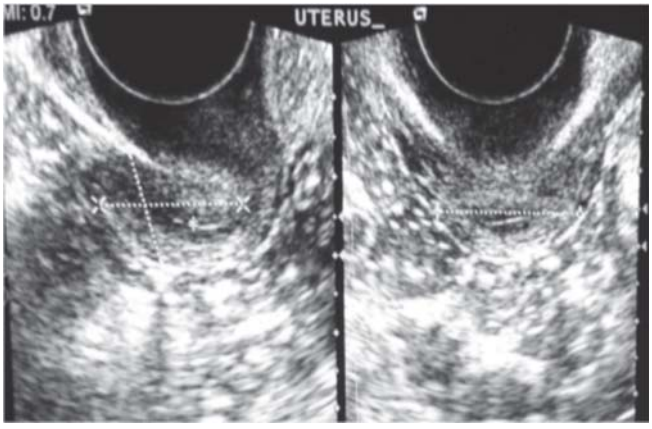

Figure 6B. Transvaginal ultrasound showing measurement of the uterine corpus. The corpus was anteflexed and infantile measuring 2.0cm x 2.3cm x 1.5cm. The endometrial lining is thin.

Transvaginal ultrasound showed an infantile uterus, thin endometrium (0.50 cm) and streak gonads (Figures 6A to 6F). Chest x-ray was normal. Hormone levels revealed an elevated follicle-stimulating hormone (FSH) at 48.01 mIU/mL and luteinizing hormone (LH) at 15.42 mIU/mL and a low level of estradiol at 7.91 pg/mL. Serum testosterone levels were normal (14.24 ng/dL). Karyotype study (Figure 7) revealed a normal male 46,XY. Fluorescent in situ hybridization (FISH) test specific for the SRY gene mutation was not available in the country.

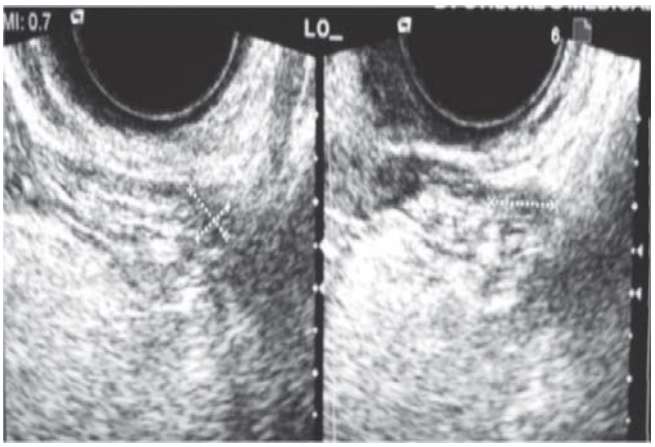

Figure 6C. Transvaginal ultrasound showing measurement of the left gonad. The left gonad measured 0.7cm x 0.9cm x 0.6cm. It is devoid of follicles.

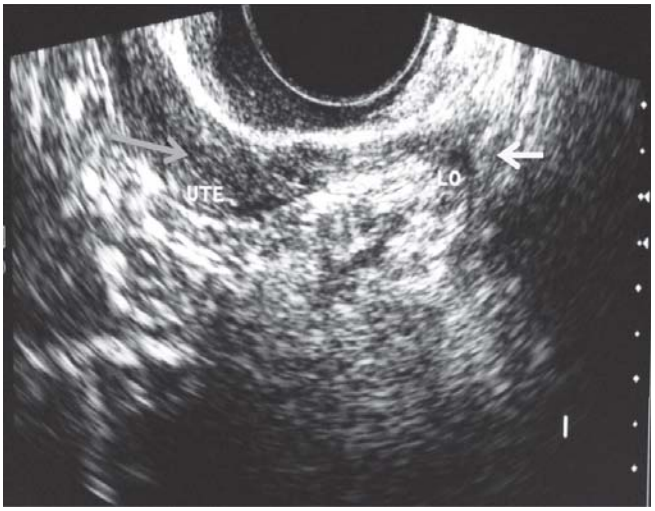

Figure 6D. Sonographic relationship of the left gonad with the uterine corpus. The red arrow showing the infantile uterine corpus and the yellow arrow showing the left gonad.

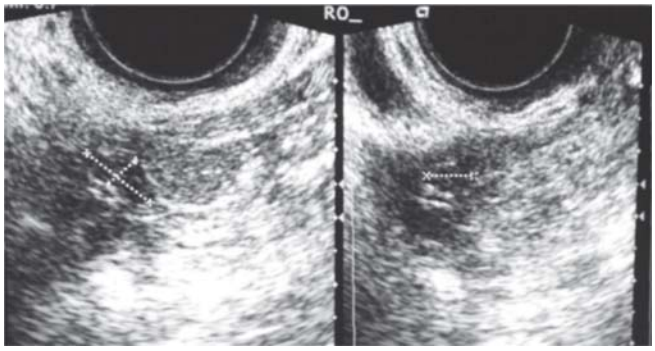

Figure 6E. Transvaginal ultrasound showing measurement of the right gonad. The right gonad measured 1.1cm x 0.7cm x 0.5cm. It is devoid of follicles.

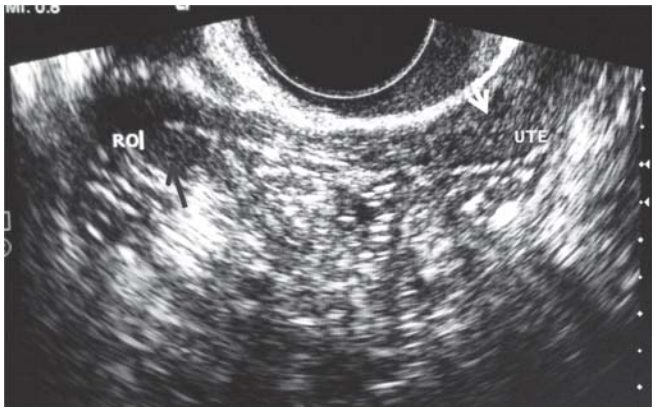

Figure 6F. Sonographic relationship of the right gonad with the uterine corpus. The white arrow showing the infantile uterine corpus and the black arrow showing the right gonad.

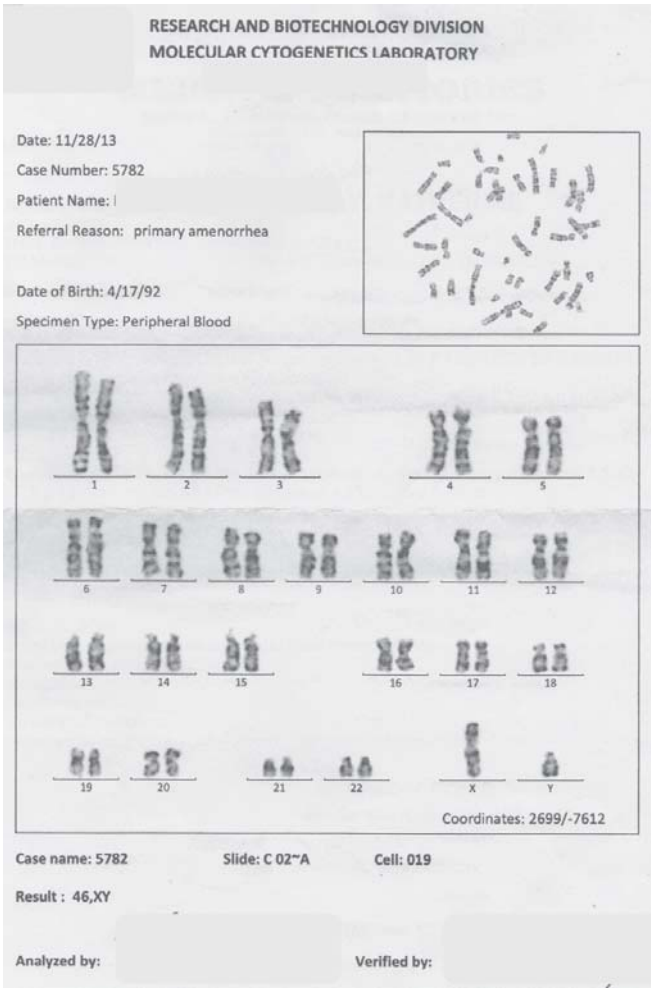

Figure 7. Karyotype of the index patient. The result shows a normal male 46, XY karyotype.

She was given hormone replacement therapy (HRT) in the form of Drospirenone 2 mg / Estradiol hemihydrate 1 mg (Angeliq^{R}) for 6 cycles from the previous consult. No menses occurred but she noted that her breasts began to develop and pubic hair slowly grew. The patient had her first menstruation after 3 months of OCP.

The patient eventually revealed to her partner that she is genetically male and that she could not bear children. The relationship ended. Presently, she desires and hopes to have children if possible.

Her bone densitometry showed that her BMD levels are within the expected range for her age (Figure 8).

Patient underwent laparoscopic bilateral gonadectomy + salpingectomy. Intraoperatively, the uterus was very small with no adhesions (Figure 9); bilateral fallopian tubes were grossly normal looking with multiple paratubal cysts on its fimbrial end on both sides (Figures 10 & 11); the right gonad was small measuring 1cm x 1cm while the left was a streak gonad (Figures 10 & 11); the cul de sac was not obliterated. The rest of the abdominal organs, including the liver and gallbladder were grossly normal.

Final histopathology result was as follows: Right gonad: Gonadoblastoma; No definite lymphovascular invasion seen; Right fallopian tube: unremarkable with paratubal cysts; Left gonad: cauterized fibrous tissue;(Left fallopian tube: unremarkable with paratubal cysts. Immunohistochemical stain results support he diagnosis of gonadoblastoma: SALL4 – positive among germ cells(PLAP – positive among germ

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NUCLEAR MEDICINE

1409133556 Apr-17-1992 22 year/s F

SPECIMEN NO.

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ROOM/BED	REFERRING PHYSICIAN	DATE/TIME OF EXAM	DATE OF REQUEST	OR/CI No.
OPD		10 31 2014 03:14 PM	10 20 2014 08:47 AM	0036141007786283

BONE DENSITOMETRY

Dear Doctor,

our patient [redacted] a BMD test on 10/31/2014 using the Lunar iDXA manufactured by GE Healthcare. The following are her risk factors for osteoporosis: Amenorrhea, Asian race.

Scan Site	Region	BMD	T-Score	Percent	Z-Score	Percent
AP Spine	L1-L4	0.883 g/cm²	-1.9	79 %	-1.9	79 %
Dual Femur	Total Right	0.746 g/cm²	-1.7	78 %	-1.7	78 %
Dual Femur	Total Left	0.745 g/cm²	-1.7	78 %	-1.7	78 %

ASSESSMENT:

Based on the ISCD recommendation of using Z-scores for premenopausal women, your patient's BMD measurements are within the expected range for her age.

RECOMMENDATIONS:

Regular weight-bearing and muscle-strengthening exercises, as well as adequate daily intake of calcium and vitamin D are recommended.

FOLLOW-UP:

Based on these results a follow-up exam is recommended after one year.

Scan interpretation criteria and values obtained are based on the recommended guidelines of the ISCD/WHO. Should you need data beyond what is recommended, please do not hesitate to call us, as these data are stored in our database.

This nuclear medicine report is part of the overall assessment of a patient's condition and best explained by the attending physician to the patient since correlation with clinical, laboratory, and other ancillary parameters may be necessary for a comprehensive analysis.

[redacted] [redacted]

NUCLEAR MEDICINE PHYSICIAN/ RADIOLOGIST CHAIRMAN, NUCLEAR MEDICINE & PET

This report has been electronically validated. No signature is required.

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Figure 8. Bone Densitometry report. The result show normal requirement for the patient age.

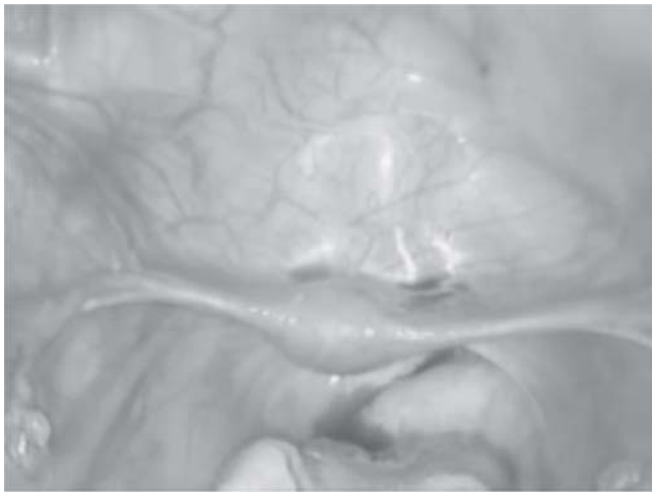

Figure 9. Laparoscopic view of the uterus. The uterus is seen suspended in the pelvic cavity; it is small in size.

cells(Inhibin – positive among supporting/ sustentacular cells.

Discussion

Evaluation of amenorrhea, like any other complaint, begins with a careful medical history and physical examination. Pregnancy should always be ruled out in any patient with amenorrhea or reproductive age.

The reproductive system has 4 distinct structural compartments: the genital outflow tract and uterus, the ovary, the pituitary and the hypothalamus. The functional integrity of each of these compartments is tested, beginning at the lowest level, and progressing systematically to the

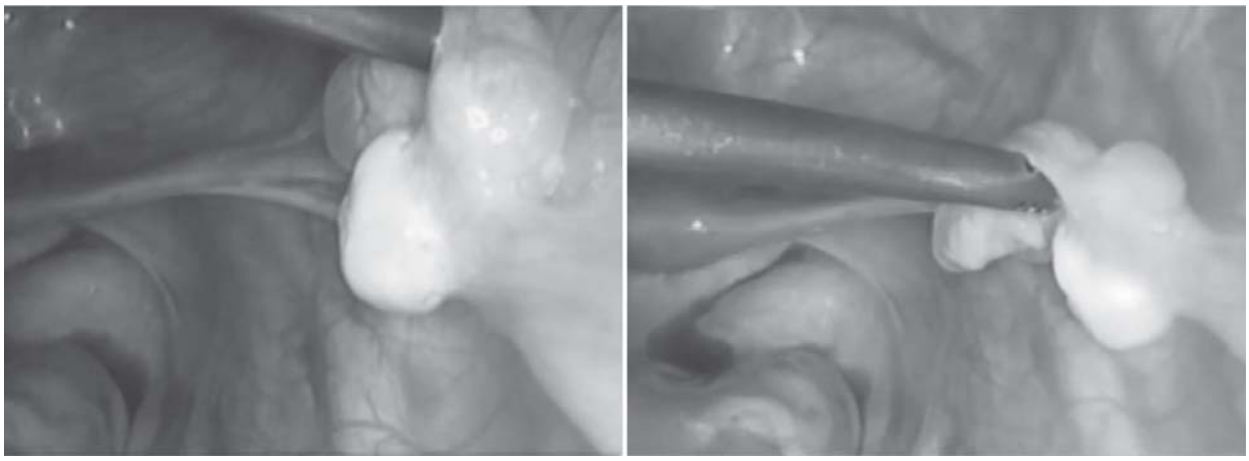

Figure 10. Laparoscopic view of the right gonad. The right gonad is small; the right fallopian tube is grossly normal with paratubal cysts on its fimbrial end. The right adnexa were noted to be lateral and somewhat distant to the uterus.

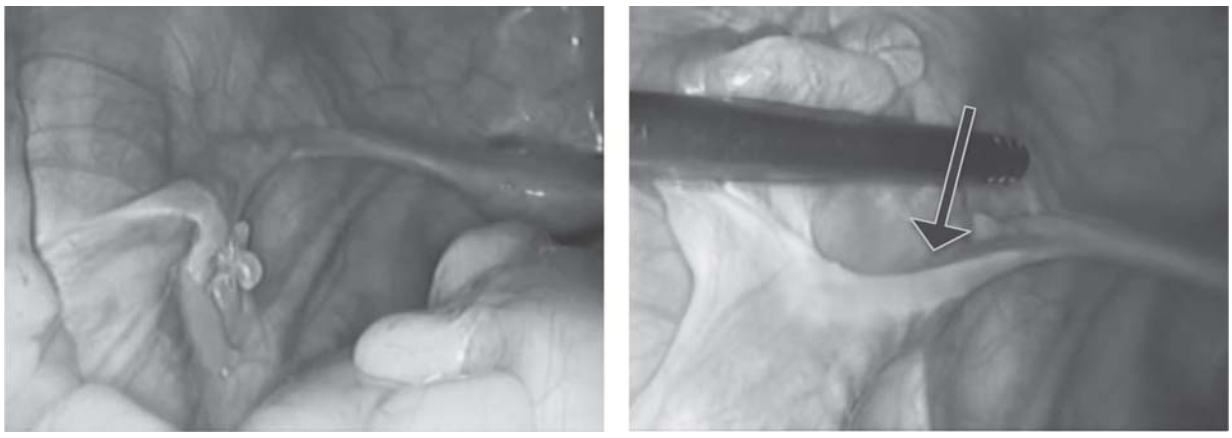

Figure 11. Laparoscopic view of the left gonad. The left gonad is streak-like (black arrow); the left fallopian tube is grossly normal with multiple paratubal cysts on its fimbrial end. The left adnexa were noted to be lateral and somewhat distant to the uterus.

higher levels of the system until the cause of amenorrhea is determined.

The overall body habitus often provides important information. Short stature and sexual infantilism are hallmarks of gonadal dysgenesis. Low body weight frequently is associated with hypothalamic amenorrhea resulting from poor nutrition (eating disorders, malabsorption syndromes) or physical, psychological, or emotional stress. Obesity or an increased waist-hip ratio (>0.85) are common features of women with PCOS.

The pattern of hair growth should also be examined. Tanner staging for breast development is a reliable indicator of estrogen production/ non-production or exposure to exogenous estrogen. An arrest in breast development suggests a disruption of the hypothalamic-pituitary-ovarian (HPO) axis.

An abdominal examination should also be done to exclude any masses such as ovarian neoplasm or uterine masses. Growth of midline hair in the infraumbilical region suggests hyperandrogenism. Abdominal striae raise the possibility of Cushing syndrome.

Examination of the external genitalia and lower genital tract is key. The presence of pubic hair growth reliably reflects androgen production or exposure. Because breast development and growth of pubic hair typically progress in a symmetrical manner, their Tanner stages should be consistent. If speculum exam is feasible, it should be performed. A patent vagina and normal cervix excludes mullerian/ vaginal agenesis, Androgen Insensitivity Syndrome (AIS) and obstructive causes of amenorrhea such as imperforate hymen or a transverse vaginal septum. A rectal examination should also be done to detect any distended hematocolpos that may form above the obstruction.

The next step in evaluation is imaging of the pelvis to determine presence or absence of reproductive organs. Transvaginal ultrasound of our index patient revealed an infantile uterus, atrophic endometrium and non-visualized ovaries (Figures 6A to 6F). Sonographically, streak gonads are not usually seen. With this initial result, an impression of gonadal dysgenesis was in mind. Confirmatory hormonal assays showed an elevated FSH and LH and a low estradiol suggesting a hypergonadotropic hypogonadism state. This is the usual finding in a patient with premature ovarian insufficiency and menopause.

The key to diagnosing gonadal dysgenesis is to perform a karyotype analysis. There are at least four categories of XY females with disorders of gonadal development.[5] Females with pure gonadal dysgenesis have female external genitalia, a small uterus, fallopian tubes, and streak gonads. This kind of disorder should be distinguished from a patient with AIS, who also presents with primary amenorrhea and an XY karyotype. The absence of breasts, and the presence of a uterus exclude this possibility in this case.

Most secondary sex characteristics do not develop because of the inability of the streak gonads to produce estrogen and androgens at normal levels. In this case, the patient has no secondary sexual characteristics such as breast development, widening of the pelvis and hips and menstruation on initial evaluation. The lack of estrogen is responsible for the deficiency in breast development, underdeveloped pelvic area and absence of menstruation. Small amounts of androgens are produced by the adrenal glands, which are not affected by the syndrome. Because of the small amount of androgens, they will only grow modest quantity of pubic hair. Patient was given HRT treatment and was able to continue it for 6 cycles. She observed an increase in breast size and growth of pubic hair to Tanner stage 2.

The importance of early diagnosis of this case is necessary due to the high possibility of developing gonadal malignancy. The risk of gonadoblastoma and dysgerminoma in women with this syndrome has been estimated to be between 15 to 35%, and current practice is to perform bilateral gonadectomy as soon as the diagnosis is made.[5] It is thought that gonadoblastomas arise from persisting undifferentiated gonadal tissue within the dysgenetic gonad.[19] This was explained to the patient and she agreed to the planned surgical procedure.

Intraoperative findings show an infantile uterus and small gonads. The gonads were located almost at the pelvic sidewall and infundibulopelvic ligament. Final histopathology was

gonadoblastoma on the right while the left gonad was a cauterized fibrous tissue. Immunohistochemical stains confirmed the diagnosis of a germ cell tumor.

How come the patient is phenotypically female even without a functioning gonad? Despite the presence of a Y chromosome, the phenotype is female because the dysgenetic (streak) gonads produce neither AMH nor androgens. In approximately 10–15% of patients, the disorder results from an inactivating mutation in the SRY gene, but in most, no cause can be identified. Absence or mutation of the SRY gene will cause development of the female reproductive organs.

The detection of the SRY gene mutation was not requested in this case. This utilizes a special test called the Flourescent in situ hybridization (FISH) analysis. This test identifies certain regions on chromosomes using fluorescent DNA probes. FISH analysis can find small pieces of chromosomes that are missing or have extra copies. These small changes can be missed by the overall karyotype test.[20] FISH test for determination of mutation of the SRY gene is not available in the country. It is not anymore necessary to determine whether this patient has this gene mutation. Management of the case will not change whether there was an SRY gene mutation or not. A mutation in the SRY gene was estimated to be at 10- 15% in Swyer's syndrome. The other 85-90% are other gene mutations that have been identified.[6]

The patient is 5 ft. and 8 inches tall. Her sister and both her parents are of average height, although her paternal grandfather stood over 6-feet. In a study by Michala, et al.[8] a characteristic and often differentiating feature of women with Swyer syndrome is their increased adult height. This may probably be secondary to the effect of the Y chromosome and the possible low levels of sex steroids that allow for a delayed epiphyseal closure.

Initiation of hormone replacement therapy is warranted to maintain bone mineral density and development of the breasts and improve uterine size for possible future pregnancy. To achieve pubertal development, a daily dose of 0.625 mg to 1.25 mg conjugated equine estrogen is given for 3 to 6 months. A maintenance therapy of the following should be given once breast and pubic hair development is achieved: 1) 0.625 mg conjugated estrogen + medroxyprogesterone acetate 10 mg, or 2) ready HRT preparation, or 3) OCP containing 30 or 35 mcg estrogen. Proper advise on medication compliance should be stressed.

Adequate sex hormone secretion during puberty has an important action on bone mineral content and metabolism.[21] Since the patient came to us with primary amenorrhea at 22 years old, an investigation on her bone integrity is warranted. A baseline Dual Energy X-ray Absorptiometry (DEXA) should document presence of osteopenia or osteoporosis. Some studies showed that the vertebral bodies of young women with hypogonadal amenorrhea have a bone mass 20 % to 30% lower than menstruating women of the same age group.[22,23] Hormone therapy and calcium supplementation are the mainstays of treatment.

There are several reported cases of successful pregnancies for women with Swyer Syndrome.[8,18,24] One study presented a successful pregnancy with oocyte donation and IVF after a debulking staging surgery with uterus preservation and adjuvant chemotherapy.[25] The patient was counseled regarding in-vitro fertilization using donor oocyte.

Conclusion

This is a rare case of complete gonadal dysgenesis (46,XY) or Swyer syndrome presenting as primary amenorrhea with absent secondary sexual characteristics at age 22. Early diagnosis is crucial in the initiation of treatment to prevent bone demineralization and initiate development of secondary sexual characteristics and menstruation. Gonadectomy is advised as soon as diagnosis is established because of high risk of gonadal malignancy. The possibility of normal conception is remote but embryo transfer from a donor oocyte is an option. Management of Swyer syndrome generally should involve induction of puberty with estrogen to develop secondary sexual characteristics and long-term combined replacement therapy with estrogen and progesterone. An abdominal MRI is recommended to determine if ectopic gonads exist. If the patient decides not to undergo surgery, monitoring for

formation of gonadal malignancy is done thru either transvaginal ultrasound or lower abdomen MRI. These patients should also be counseled on the psychological aspects of the disease. Moral support from family members and professionals is crucial. Giving the patients the right knowledge about their condition could limit the risk of psychological problems and is important for satisfactory development into adulthood.

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