A case of ovotesticular disorder of sexual development (45 XO/46 XY: mosaicism versus chimerism)*

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ABSTRACT

Ovotesticular disorder of sex development (OT-DSD), previously known as true hermaphrodite, is a rare disorder of sexual differentiation in which the gonads of an individual are characterized by the presence of both mature ovarian and testicular tissues. The diagnosis has traditionally been applied only if an individual has 1) histologically verified ovarian follicles or proof of their prior existence (e.g. corpora albicantia) and 2) seminiferous tubules or spermatozoa. This paper introduces you to a 14 year-old, who presented with primary amenorrhea and enlarging abdominal mass, underwent exploratory laparotomy, salphingooophorectomy, histologically diagnosed as a possible case of a true hermaphrodite and chromosomally diagnosed as 45XO/46XY who developed endodermal sinus tumor, a germ cell tumor, considered highly malignant.

Keywords: Chimerism, endodermal sinus tumor, mosaicism, Ovotesticular Disorder of Sex Development (OT-DSD), true hermaphrodite, 45X/46XY

INTRODUCTION

The disorders of sex development (DSD) is an uncommon disorder with an incidence of 1:4500 to 1:5000 live births[1]. True hermaphrodite (Ovotesticular DSD) is responsible for 4% to 10% of cases of DSD but this is the most common type of intersex disorder among South African blacks. The frequency of different karyotype found among true hermaphrodite are 46 XX (60%), 46 XX/46 XY (30%), and 46 XY (<10%)[2]. In a study by Bhansali *et al*. from a tertiary care center in India, only one case of 46 XY Ovotesticular DSD was detected among seven true hermaphrodite patients over 10 years.

A majority of true hermaphrodite patients present with genital ambiguity with or without palpable gonads[3]. However, the appearance of external genitalia varies from normal female with mild clitoromegaly to normal male.

The important issue related to intra-abdominal testicular tissue is the risk of development of gonadal tumor, e.g. gonadoblastoma. The risk is more in cases of gonadal dysgenetic syndromes compared to true hermaphrodite (15% to 35% vs. 0.2% to 0.4%)[4,5]. As the true hermaphrodite is itself a rare disease and most of the cases have 46 XX karyotype, the exact risk of development of gonadal tumor among 46 XY Ovotesticular DSD is not known. In most of the patients with true hermaphroditism, the diagnosis is made by the pathologist only after gonadectomy. However, it is important to retain at least the ovarian tissue in case of true hermaphrodite patients with uterus as few cases with successful pregnancy are reported in the literature[6].

Ovotesticular disorder of sex development or true hermaphroditism should be kept as one of the differential diagnosis of primary amenorrhea particularly in the presence of hyperandrogenism. Detailed physical examination and step-wise investigations including karyotype will pick up these cases. Various factors including the possible diagnosis (gonadal dysgenesis vs. true hermaphrodite), presence of Y-chromosome, sex of rearing and the scope of fertility should be taken into consideration before doing gonadectomy[7].

CASE

General Data

This is a case of M.D., 14 years old, nulligravid, single, Catholic, elementary undergraduate, currently residing in Bacoor, Cavite, who consulted due to dyspnea.

Past Medical History

In 1994, when she was 4 months old, she was hospitalized for 4 months due to jaundice with a diagnosis of gall bladder disease for which blood transfusion and phototherapy were done. At 6 years-old, the patient had her first episode of rigidity of the extremities with no other associated signs and symptoms. There were no medications taken nor consultations done. At age 10, she had tonic-clonic body rigidity associated with upward rolling of the eyeballs which happened about every 3 months. Due to financial constraints, the patient was not brought to a physician for consultation hence her condition was not diagnosed and no medications were

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started. The patient has no bronchial asthma, hypertension, or previous trauma or allergy to food and drugs.

Family History

There is no hypertension, diabetes mellitus, cancer, bronchial asthma, heart disease or history of developmental delay in the family.

Personal and Social History

The patient is an elementary under graduate (grade 1) who has no vices and no coitus. According to the mother, she loves to play basketball. She is living with her parents and four siblings. Her father is a coal vendor while her mother is a housewife.

Menstrual History

Patient has no menarche yet.

Obstetric History:

Patient is nulligravid.

Prenatal and Birth History

The patient's mother had no prenatal check-ups, no intake of folic acid, multivitamins nor ferrous sulfate. Her mother had diarrhea, vomiting and fever for 3 days at 4 weeks age of gestation wherein she took loperamide and paracetamol. She was delivered full term at home via spontaneous vaginal delivery, unremarkable, by traditional birth attendant. Neonatal period was uneventful.

Immunization History

The patient had BCG at 4 months old. No other vaccines such as MMR, hepatitis vaccines, polio vaccines or diphtheria vaccines were given.

Nutritional History

The patient is breastfed for 4 months. Complementary food was introduced and tolerated at 7 months. Daily diet includes fish, vegetables and occasionally poultry and pork.

Developmental History

The patient's developmental milestone was at par with normal child until she was 6 years-old when her parents noticed slurring of speech which they attributed to the episodes of seizure during this time. At 8 years-old, the patient entered Grade 1 and according to her teacher, she cannot cope up with the teaching modules and is delayed compared to her classmates. This prompted her parents to stop her from schooling.

History of Present Illness

Eight weeks prior to admission, the patient's mother palpated a hypogastric mass on the patient's abdomen after she complained of pain in urination. No hypogastric pain, no changes in bowel movement, no fever associated. She was then brought to a local health center where urinalysis done and showed urinary tract infection. She was prescribed with cotrimoxazole 400/80mg tab which the patient took twice a day for 7 days. This afforded relief of dysuria.

Six weeks prior to admission, the patient's mother noticed that the mass was enlarging. No other associated signs and symptoms. No consult done. No medications taken.

Five days prior to admission, with the persistently enlarging mass, there was recurrence of dysuria now associated with hypogastric pain. She was given paracetamol for the pain which afforded temporary relief.

Four days prior to admission, still with enlarging abdominal mass and dysuria, patient had bipedal edema. No consult done. No medications taken.

On the day of admission, the patient experienced difficulty of breathing prompting consult and subsequent admission.

Review of Systems

The patient's mother reported approximately 15% weight loss with associated decrease in appetite. There were no rashes, no lymphadenopathy, no easy bruising and bleeding. Cardiovascular wise, there were no cyanosis, no chest pain, no palpitations noted. Furthermore, there were no coughs, no colds, no diarrhea, no constipation, no vomiting nor hematemesis. There was neither body weakness nor joint pain. However, the patient's parents reported that there was increase in seizure frequency, from previously once a month, became thrice a month.

Physical Examination

Upon admission, the patient was conscious, coherent, oriented to time, place and person, ambulatory and slightly tachypneic with respiratory rate of 28 cpm. The patient was febrile at 37.8^{o}C and tachycardic at 118 bpm. She has short stature (136cm) with weight of 39 kg and BMI of 21.2kg/m^2. She had dry skin, anicteric sclera and pale palpebral conjunctiva. There was no cervical lymphadenopathy or tonsillopharyngeal congestion appreciated. She had symmetrical chest expansion, clear breath sound, adynamic precordium and no murmurs heard. On abdominal examination, the abdomen was globular (abdominal girth = 96cm), firm, with a 20 x 25 cm solid, non-tender mass, with cystic areas and limited mobility located at the suprapubic area extending up to 3 cm below the subxiphoid process. On pelvic examination, she had normal external genitalia, intact hymen but an enlarged clitoris (Figure 1), with clitoral size of 2.5cm in length, was noted. On digital rectal examination, she had

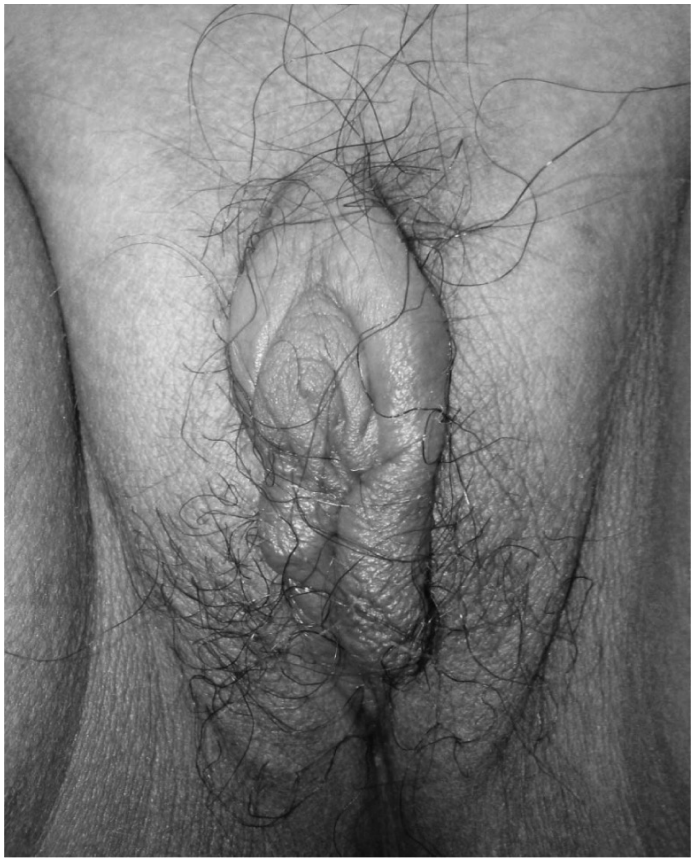

Figure 1. External genitalia of patient M.D.

good sphincteric tone and intact rectal vault. There were no intraluminal masses appreciated, the cervix and uterus were not palpable and the mass was not palpable in the cul-de-sac. Neurologic examination showed that she has no motor and sensory deficits and deep tendon reflexes were normal. Important to note is that, there was delay in secondary sexual characteristics. Only the papilla was elevated hence breast was graded as Tanner Stage 1 (Figure 2) while pubic area shows small amount of long, down hair with slight pigmentation on the labia majora hence, Tanner Stage 2 (Figure 3). There was also absent axillary hair (Figure 4).

Laboratory Results

Laboratory results showed that the patient has hypochromic, microcytic anemia with hemoglobin of 60 mg/dL, MCH of 24.3 and MCHC of 295. There was also leukocytosis of 20.32 with neutrophil predominance (85%) (Table 1). Urinalysis was normal (Table 2) while blood chemistry showed elevated creatinine and hypokalemia (Table 3). Chest x-ray was done which showed essentially normal chest findings (Figure 5). Transrectal ultrasound (Figures 6, 7 and 8) showed no normal uterus and ovaries seen. Occupying the pelvic cavity is a well circumscribed, solid mass measuring 12.8 x 13.4 x 10.4 cm, with cystic spaces on the superior portion. Color flow mapping of the

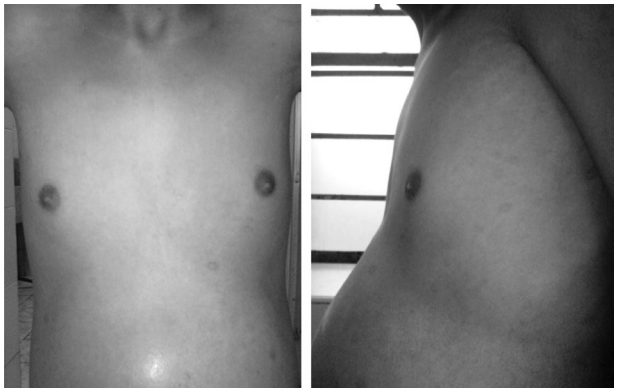

Figure 2. Breast papilla of patient M.D. showing a Tanner Stage 1 for breast

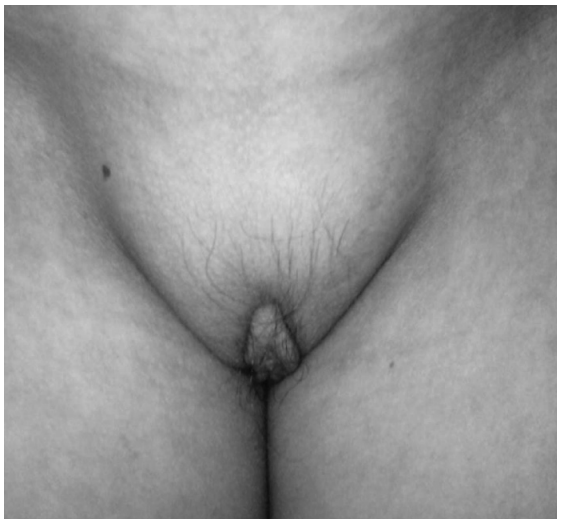

Figure 3. Small amount of long, downy hair on patient M.D.'s pubic area showing Tanner Stage for pubic hair.

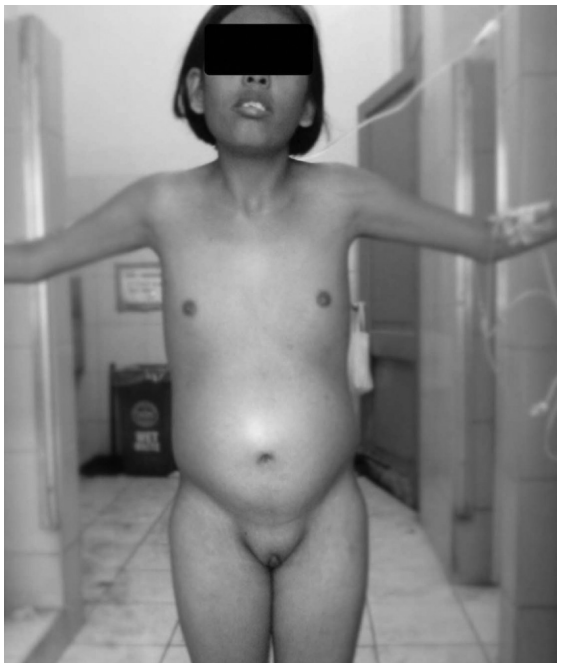

Figure 4. Patient M.D. showing delayed secondary characteristics (breast papilla, small amount of pubic hair and absence of axillary hair)

Table 1. Complete blood count of patient M.D. (1/2/14)

RBC	2.45
WBC	20.32 (High)
Platelet	870
Hgb	60 (Low)
Hct	0.202
MCV	82.5
MCH	24.3 (Low)
MCHC	295 (Low)
Neutrophil	0.85
Monocyte	0.10
Lymphocyte	0.04
Eosinophil	0.01

Table 2. Urinalysis of patient M.D. (1/2/14)

Color	Yellow
Transparency	Clear
Specific Gravity	1.015
pH	6.0
Protein	Trace
Sugar	negative
RBC	0-1
WBC	1-2
Epithelial cells	Occasional
Bacteria	+1

Table 3. Blood chemistry of patient M.D. (1/5/14)

BUN	7
Crea	161 (High)
Na	133
K	2.3 (Low)
Cl	98
Ca	2.02
Mg	0.79
AST	17
ALT	38
Albumin	19
Uric acid	0.33

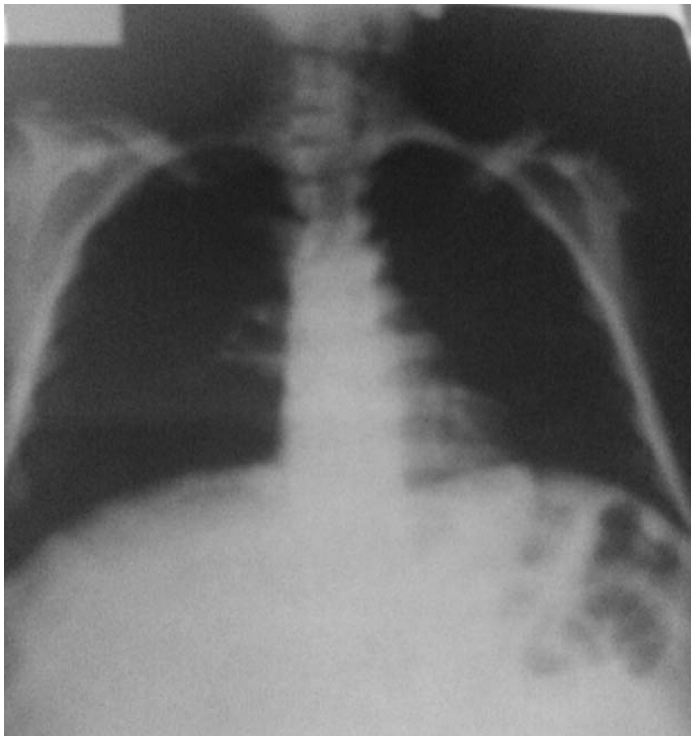

Figure 5. Showing normal chest findings

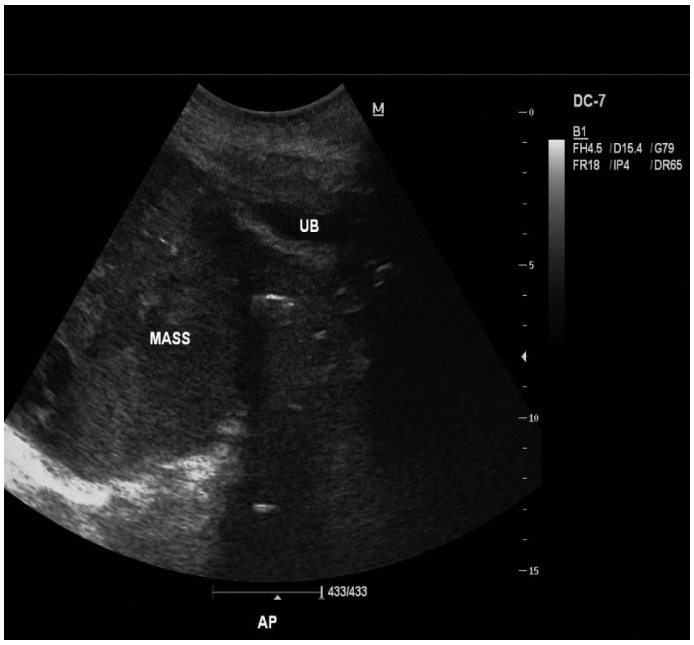

Figure 6. Showing no uterus and ovaries.

solid mass shows scanty central vascularity. The impression of the sonologist was pelvic mass, consider uterine mass versus ovarian new growth probably malignant (Sassone = 13, Lerner = 8, IOTA: Solid, Color Score of 2). The patient was subsequently admitted with the following admitting diagnoses: 1. Abdominopelvic mass, probably malignant; 2. Primary amenorrhea; 3. Seizure disorder; 4. Global developmental delay and 5. Anemia probably secondary to chronic disease.

Course in the wards

The patient was admitted for work-up and management of her symptoms. She was transfused with 4 units of packed red blood cell which increased the hemoglobin from 60 mg/dL to 134 mg/dL and hematocrit from 0.202 to 0.43. Hypokalemia was also corrected by giving Plain Saline added with Potassium Chloride 40 milliequivalents. She was referred to different services including the Reproductive-Endocrinologic-Infertility (REI),

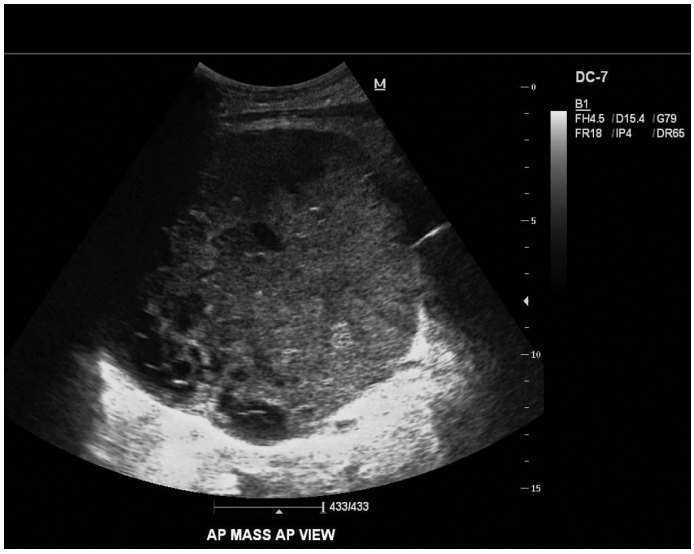

Figure 7. Abdominopelvic mass (AP View) showing multiple cystic spaces on the superior portion.

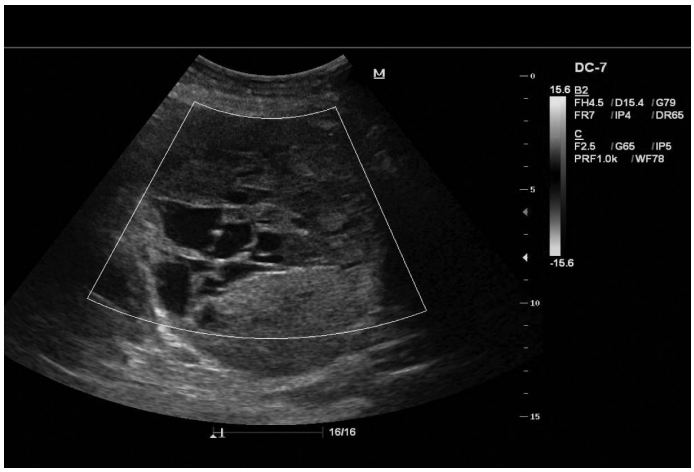

Figure 8. Color flow mapping of the mass showing scant central vascularity

Pediatric Neurology and General Pediatrics Services for further evaluation and for co-management. Since the patient presented with primary amenorrhea, peripheral blood is sent for karyotyping. Blood samples for tumor markers such as LDH, AFP and CA-125 were sent to the laboratory which showed elevated values while beta-HCG and CA 19-9 were low and normal, respectively. Serum gonadotrophin hormones such as FSH, LH and estradiol were elevated while serum testosterone was low (Table 4). Holoabdominal ultrasound results showed an abdominopelvic mass, likely ovarian or uterine in origin, a hepatic focus at segment IVB, worrisome for metastasis if with proven primary malignancy, bilateral pelvocaliectasia and left renal cyst. The REI Service was considering that the primary amenorrhea is probably secondary to androgen insensitivity syndrome and that the abdominopelvic mass was probably a gonadoblastoma. The Pediatric Neurology Service diagnosed the patient with epilepsy, localization-related with secondary generalization and global developmental delay. Valproic acid 478 mg/tablet, 1 tablet once a day and Diazepam 5 mg IV as needed were started. Since the patient was also persistently tachycardic, hyperthyroidism was considered by Pediatrics Service. Free T4 and TSH were requested but results showed normal values (Table 5) hence hyperthyroidism was ruled out. After the patient was hemodynamically prepared, she was scheduled for operation. She underwent exploratory laparotomy, adhesiolysis, left salphingo-oophorectomy and infracolic omentectomy. Intraoperatively, there was minimal ascites noted. There was a 1.5 x 1.0 x 0.5 cm muscular structure at the pelvic region which seems to be an infantile uterus (Figure 9). To the right of this muscular structure is a tube-like structure with attached gonadal streak measuring 1.5 x 0.3 cm (Figure 10). Furthermore, the left gonad was converted to a uniloculated mass measuring 18cm x 20cm x 17cm with solid areas and sero-sanguinous fluid inside (Figures 11 and 12). The said mass was very adherent to the bowels and omentum (Figure 13), hence, the rectum was inadvertently transected during adhesiolysis (Figure 14). Hartmann's procedure and JP drain insertion were performed under general anesthesia. Palpation of the other abdominal organs revealed multiple 1 x 1 cm firm masses on the liver surface. The estimated blood loss was 1800 ml wherein two units packed RBC was transfused during the operation. The patient was maintained on NPO until the 5th post-op day when sips of water was started and tolerated by the patient. Post-operatively, patient's blood pressure

Table 4. Tumor markers and gonadotrophin hormones of patient M.D.

Tumor markers	Patient's values	Normal values
LDH	5,946 (High)	<500
AFP	>500 (High)	1.09 – 8.04ng/ml
CA -125	208 (High)	0 – 35
Total β-HCG	<2.39 (Low)	5 – 25
CA 19-9	3.6 (Normal)	0 – 3.7
Serum testosterone	3.4 (Low)	270-1070 ng/dL
FSH	55.5(High)	0.6 – 9.5 mUI/ml
LH	57 (High)	0.7 – 9.0 mUI/ml
Estradiol	305.1 (High)	<20 pg/ml

Table 5. Thyroid hormones of patient M.D.

FT4	21.3 (Normal)
TSH	2.8 (Normal)

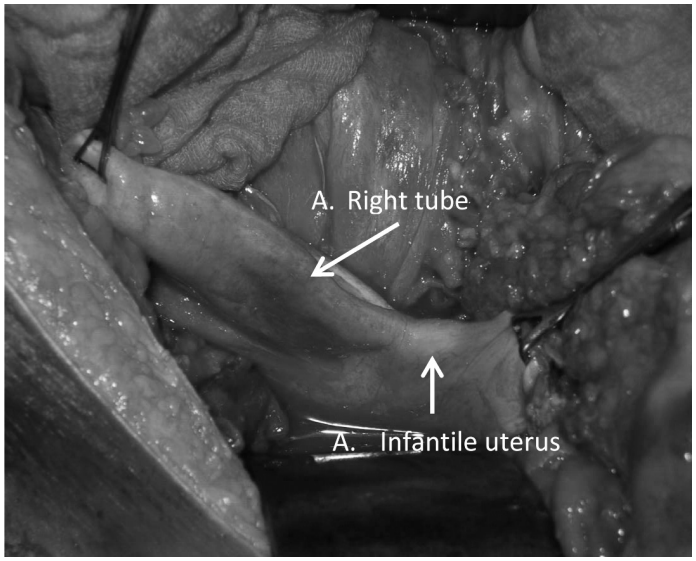

Figure 9. A. Infantile uterus measuring 1.5cm x 1cm x 0.5cm B. Right tube which appeared normal

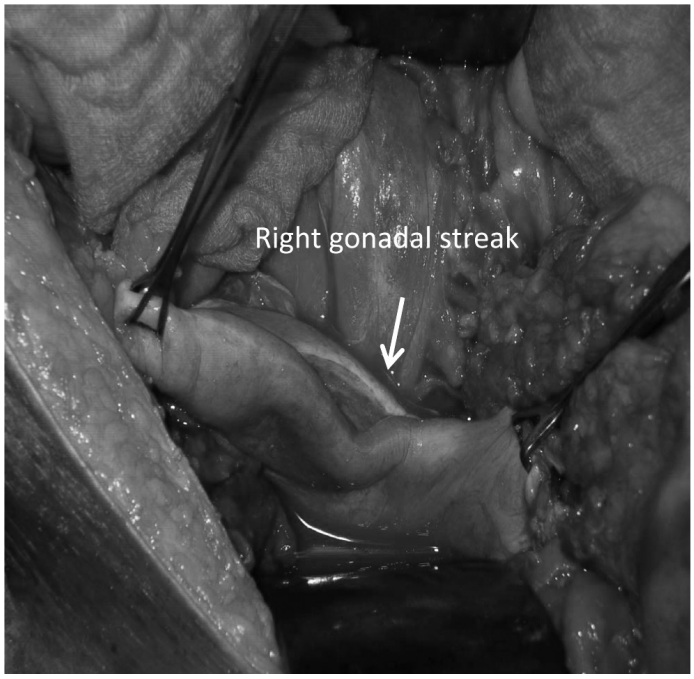

Figure 10. Gonadal streak measuring 1.5cm x 0.3cm

was noted to be constantly elevated at 130-140/80-90 mmHg. She was referred to Pediatrics Nephrology Service, Pediatric Endocrine Service and Pediatric Hema-Oncology Service. Amlodipine 5mg/tablet and Enalapril 10mg/tablet once a day were given as anti-hypertensive medications. Serum K^+ was also noticed to be persistently below normal values (lowest value: 1.6 mmol/L) with associated increase in serum sodium (highest valueL 181 mmol/L). Because of these, secondary hyperaldosteronism with hypernatremic dehydration was entertained. Serum aldosterone, renin and cortisol were done. Results showed elevated values of the three hormones (Table 6). Potassium deficit was

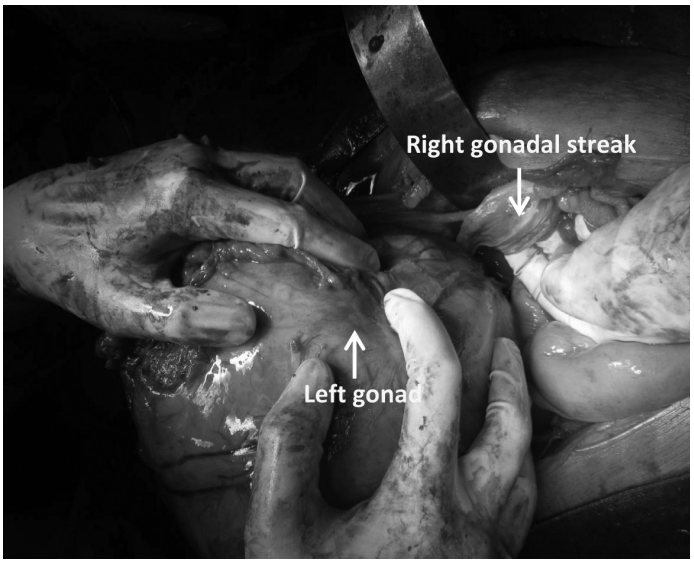

Figure 11. Left gonad converted to 18cm x 20cm x 17cm mass, multi-septated, multi-loculated with solid areas and serous-sanguinous fluid inside

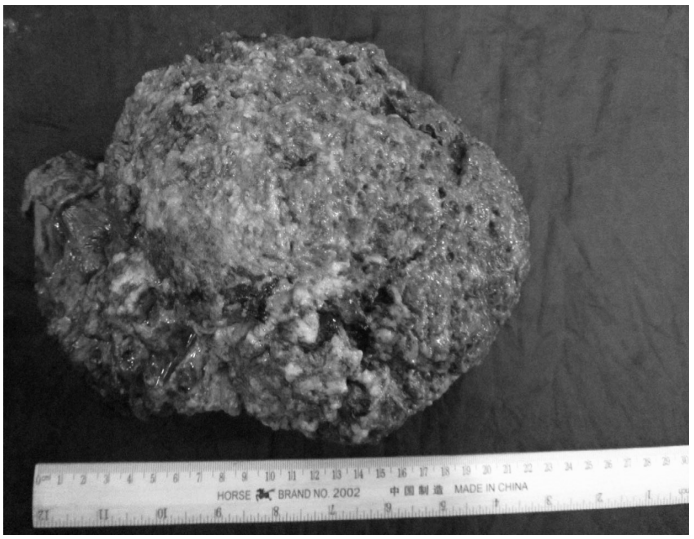

Figure 12. Cut section of the left gonad

Figure 13. Omental segment of patient M.D.

Table 6. Different hormones of patient M.D.

Hormones	Patient's values	Normal values
Aldosterone	>2,000 pg/ml	12 – 340 pg/ml
Renin	16.2 ng/ml	0.5 – 1.9 ng/ml
Cortisol	1,094.9 nmol/L	138 – 690 nmol/L

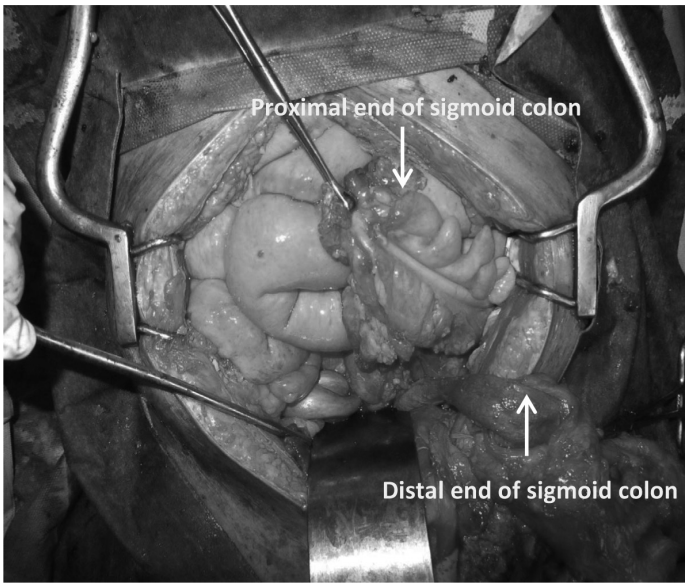

Figure 14. Bowel injury incurred during adhesiolysis of the left gonad from the sigmoid colon

corrected using potassium chloride in plain saline solution while elevated sodium was corrected using free water deficit correction and hydration with D5 0.3 NaCl. On day 15 post-op, the patient developed on and off fever with highest temperature of 39°C. Urinary tract infection with possible urosepsis was considered after urinalysis showed innumerable WBCs and urine culture showed growths of K. *pneumoniae*. ciprofloxacin 500mg/tablet twice a day was started. However, on day 20 post-op, with persistent fever, patient developed difficulty of breathing. Crackles and retractions were appreciated. Nosocomial pneumonia was the primary consideration until chest x-ray revealed normal chest findings. Dyspnea progressed hence, patient was intubated and hooked to mechanical ventilator. Meropenem 780mg IV every 8 hours was started. After 5 days of mechanical air support, due to improvement in dyspnea and resolution of crackles, patient was extubated and tolerated room air. The patient's parents and relatives were counseled by the Palliative Service and all co-managing services on the prognosis of the patient's condition. The patient's parents decided to bring her home against medical advice. After two days, the patient expired at home.

Result of karyotyping showed mosaic karyotype involving two cell lines. One cell line showed an abnormal karyotype of 45 chromosomes including a monosomy X and another cell line showed normal male karyotype, identified in 74 cells, which was confirmed by gross G-banding.

Furthermore, final histopathologic result of the specimens submitted showed endodermal sinus tumor of the left "gonad", chronic salphingitis, nonspecific fallopian tube, left, microscopic evidence of fallopian, and epididymal tissues in one tissue section. Figures 15 and 16 shows the histology of the specimen showing eosinophilic cells with vesicular nuclei and prominent nucleoli with fibrous cores of tissues. Schiller-Duval body, which is pathognomonic of endodermal cell tumor, is shown in Figure 17. Tissues of fallopian tube, epididymis and rete testis were also seen altogether in one tissue section (Figures 18-20). The pathologist commented that this case may be a possible case of true hermaphrodite though the tumor has eaten through the gonadal tissues.

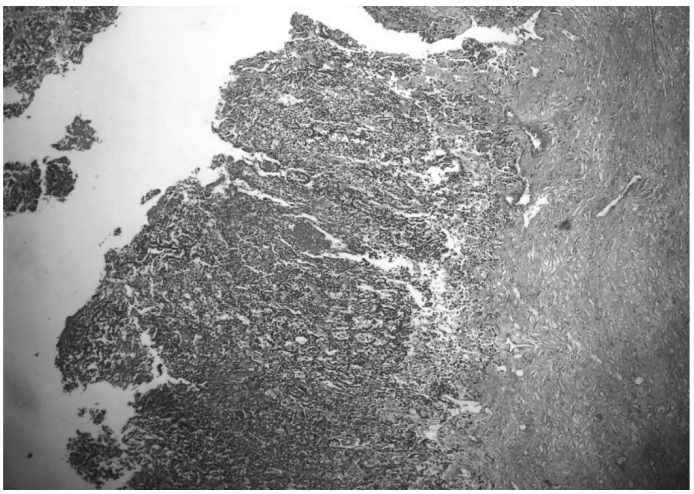

Figure 15. Scanning view of patient M.D.'s left "gonad" showing eosinophilic cells on the background of fibrous tissues characteristic of endodermal sinus tumor

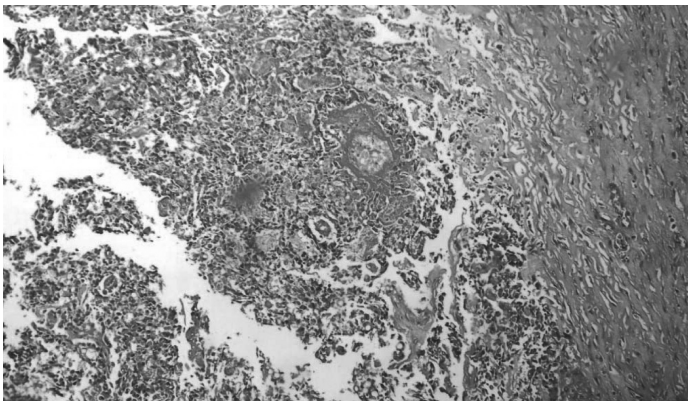

Figure 16. Low-power view of patient M.D.'s left "gonad"showing vesicular nuclei with prominent nucleoli characteristic of endodermal sinus tumor

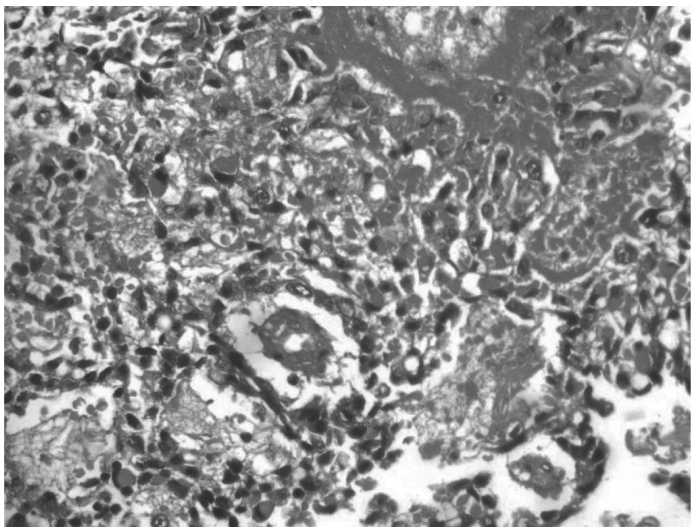

Figure 17. High-power view showing Schiller-Duval body, pathognomonicof endodermal sinus tumor. Also shown is the central capillary with visceral and parietal layer of cells resembling primitive glomeruli

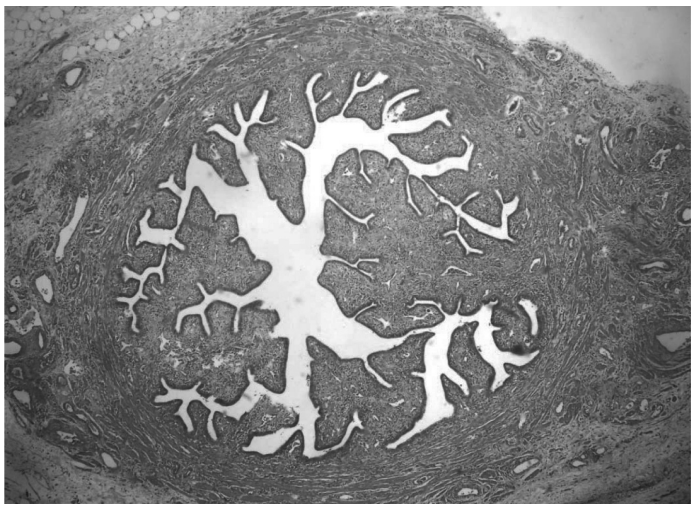

Figure 18. Microscopic cut section of patient M.D.'s fallopian tube.

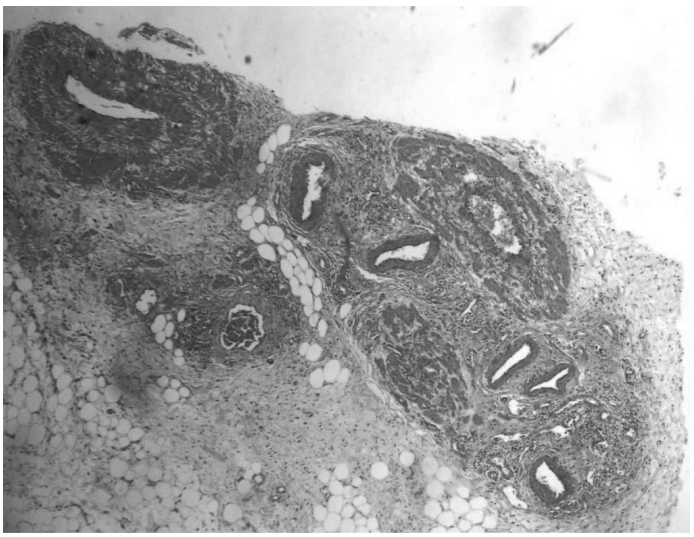

Figure 19. Microscopic cut section of patient M.D.'s rete testis.

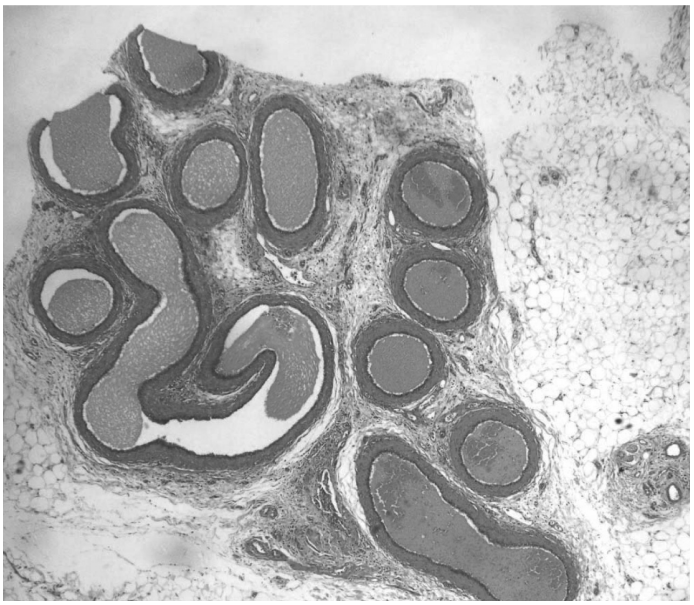

Figure 20. Microscopic cut section of patient M.D.'s epididymis.

DISCUSSION

A. Primary Amenorrhea

Primary amenorrhea, defined as the absence of menstruation during the reproductive years, is present in our patient. It can be either physiologic or pathologic (8). This could also be due to several medical conditions categorized into four groups as shown in the table below. Our patient likely fall under the category of no breast but with uterus present (Table 7).

The patient presented with features of Turner's Syndrome, a 45XO/46XY mosaicism on chromosome analysis, a contralateral gonadal streak, and both male and female reproductive tissues on the same gonad making true hermaphoditism and gonadal dysgenesis as differential diagnoses

True hermaphroditism refers to individuals who have both unequivocal ovarian tissue and testicular elements regardless of their karyotypes whereas mixed gonadal dysgenesis (MGD) refers to individuals who have a differentiated gonad on one side and a streak gonad or streak testis on the other side. Histopathologic examination of our patient's left gonad revealed fallopian tube, rete testis and epididymis in one slide making true hermaphroditism as our primary diagnosis.

B. Ovotesticular Disorder of Sexual Development (True Hermaphroditism)

True hermaphroditism is a term for a condition in which an individual is born with both ovarian and testicular tissue. There may be an ovary underneath one testicle or the other, but more commonly one or both

Table 7. Classification Disorders with Primary Amenorrhea and Normal Female External Genitalia.

I. Absent breast development; uterus present
- **A.** Gonadal failure
  1. **a.** 45,X (Turner's syndrome)
     b. 46,X, abnormal X (e.g., short- or long-arm deletion)
     c. Mosaicism (e.g., X/XX, X/XX,XXX)
     d. 46,XX or 46,XY pure gonadal dysgenesis
     e. 17α-hydroxylase deficiency with 46,XX
- **B.** Hypothalamic failure secondary to inadequate GnRH release
  1. Insufficient GnRH secretion due to neurotransmitter defect
  2. Inadequate GnRH synthesis (Kallman's syndrome)
  3. Congenital anatomic defect in central nervous system
  4. CNS neoplasm (craniopharyngioma)
- **C.** Pituitary failure
  1. Isolated gonadotrophin insufficiency (thalassemia major, retinitis pigmentosa)
  2. Pituitary neoplasia (chromophobe adenoma)
  3. Mumps, encephalitis
  4. Newborn kernicterus
  5. Prepubertal hypothyroidism

II. Breast development; uterus absent
- **A.** Androgen resistance (testicular feminization)
- **B.** Congenital absence of uterus (utero-vaginal agenesis)

III. Absent breast development; uterus absent
- **A.** 17,20-desmolase deficiency
- B. Agonadism
- **C.** 17α-hydroxylase deficiency with 46,XY karyotype

IV. Breast development; uterus present
- **A.** Hypothalamic etiology
- **B.** Pituitary etiology
- **C.** Ovarian etiology
- **D.** Uterine etiology

Lifted from Vern L. Katz, MD, et. al: Comprehensive Gynecology 5th edition.

gonads is an ovotestis containing both types of tissue[8]. In 2006, this term was replaced by Ovotesticular Disorder of Sexual Development (OT-DSD)[9]. OT-DSD, or individuals with both gonads, present with ambiguous external genitalia, the degree depending mainly on the amount of testosterone produced by the testicular tissue between 8 and 16 weeks of gestation. Our patient presented with primary amenorrhea, clitoromegaly and absence of uterus and cervix on ultrasound which on laparotomy revealed infantile uterus and right gonadal streak. The left gonad, on the other hand, was converted to an 18 x 20 x 17 cm mass, mostly solid, which on meticulous examination under microscope showed malignant transformation. Unfortunately, as described by the pathologist, the tumor (endodermal sinus tumor) has "eaten through" the gonadal tissues, hence it was not clear if it contains testicular or ovarian tissues. However, tissues of fallopian tube (female reproductive tissues) and epididymis and rete testis (male reproductive tissues) were altogether seen in a cut section of the specimen. This finding would raise the question if our patient is really a case of OT-DSD since strict definition of this condition is the presence of both unequivocal ovarian tissue and testicular elements[10]. Nevertheless, Simpson, et al. stated that the presence of fallopian tubes or vasa deferentia reflects ipsilateral gonadal composition[11]. Epidemiologically, OT-DSD is a very rare condition with the geographical distribution showing higher prevalence in the African continent, especially among South African blacks, with the number of published cases being 17 per 100 million people, followed by Europe

at 15.3. Asia is under represented at 1.2 cases per 100 million[7]. There are several ways in which OT-DSD may occur. It can be caused by the division of one ovum, followed by fertilization of each haploid ovum and fusion of the two zygotes early in development. Alternately, an ovum can be fertilized by two sperm followed by trisomic rescue in one or more daughter cells. Thirdly, two ova can be fertilized by two sperms and will occasionally fuse to form a tetragametic chimera. If one male zygote and one female zygote fuse, a hermaphroditic individual may result. Lastly, it can be associated with mutation in the SRY gene. As in our case, the actual cause of the presence of both male and female reproductive tissues is still a mystery since this can only be determined through embryology. Is our patient a mosaic or chimera?

C. 45 XO/46XY : Chimerism or Mosaicism

The chromosomal findings in OT-DSD were first reported in 1959 by Hungerford, who demonstrated a 46, XX chromosomal complement in peripheral blood lymphocytes of an individual with this disorder. OT-DSD is a genetically heterogeneous condition with the predominant karyotype being 46,XX, while 46,XX/46,XY chimerism, 46,XY karyotype, 45XO/46XY and X-Y translocation are less frequent. As in our case, karyotyping done at the Institute of Human Genetics, University of the Philippines, Manila revealed that metaphase from blood cultures showed a mosaic karyotype involving two cell lines. One cell line showed an abnormal karyotype of 45 chromosomes including a monosomy X, identified in six cells. A second cell line showed a normal male karyotype, identified in 74 cells. This corresponds to the 45XO/46XY type of chromosomal abnormalities described in cases of OT-DSD[10]. The 45XO component of this karyotype, due to the absence of an entire sex chromosome, explains the phenotypic features of our patient. Patient M.D. had short stature, broad chest, wide-spaced nipples and delayed secondary sex characteristics. Girls with Turner syndrome are said to typically experience gonadal dysfunction (non-working ovaries) resulting to amenorrhea, which is present in our patient. The presence of mosaicism is estimated to be relatively common in affected individuals (67-90%) [(12)]. *Mosaicism*[13], defined as the presence in the same individual of two or more cell lines derived from a single stem line but with different chromosomal complements is commonly contrasted from *chimerism*. The latter is defined as a single organism that is composed of two or more different populations of genetically distinct cells that originated from different zygotes involved in sexual reproduction.[14] However, as in our case, the presence of OT-DSD still remains uncertain if this is due to mosaicism or chimerism.

D. Endodermal Sinus Tumor

The patient's right gonad (possibly an ovotestis) developed malignant degeneration in the form of endodermal sinus tumor. Endodermal sinus tumor (EST), also known as yolk sac tumor (YST), is a member of the germ cell tumor group of cancers. It is the most common testicular tumor in children under 3, and is also known as infantile embryonal carcinoma. This age group has a very good prognosis. In contrast to the pure form typical of infants, adult endodermal sinus tumors are often found in combination with other kinds of germ cell tumor, particularly teratoma and embryonal carcinoma. While pure teratoma is usually benign, endodermal sinus tumor is malignant[15].

Endodermal sinus tumor cells secrete alpha-fetoprotein (AFP), which can be detected in tumor tissue, serum, cerebrospinal fluid, urine and, in the rare case of fetal EST, in amniotic fluid. Our patient has an elevated serum AFP of >500ng/ml (normal values: 1.09 - 8.04 ng/ml) supporting the histologic finding of endodermal sinus tumor.

EST can have a multitude of morphologic patterns wherein Schiller-Duval bodies on histology are pathognomonic and seen in the context of the endodermal sinus-like pattern. Cut section of patient's right gonad showed the Schiller-Duval bodies (Figure 17).

A review of 283 cases of human true hermaphroditism published from 1980 to 1992 showed that 13 patients (4.6%) developed malignant degeneration of the gonads. Occasionally more than one tumour was found in a single individual. The tumors were gonadoblastoma (6), seminoma (3), dysgerminoma (3), cystadenoma (2), Sertoli-cell-tumour (2). Teratoma, nephroblastoma and thecoma were reported once. The youngest patient with a tumor was 14 months old, the oldest 80 years. The median age at diagnosis of a tumor was 25.5 years. The tumors developed in 8 cases of ovotestis, in 3 cases of pure ovary and pure testis and in one case the type of gonad was not specified. In 6 of the 13 patients the karyotype was 46,XX, 5 had a 46,XY karyotype, one a 46,XX/46,XY mosaicism and in one the karyotype was not given[11]. Our patient is a 14-year old who was a case of true hermaphroditism with 45XO/XY mosaicism/chimerism who developed endodermal sinus tumor, a tumor not usually associated with OT-DSD, but is considered highly malignant.

E. What are the issues of having an OT-DSD?

Infants affected by OT-DSD must be assigned a sex of rearing. Karyotype, appearance of the external genitalia, type of gonads present, need for surgical interventions to provide consistency with the sex of rearing and potential for fertility, are crucial in the complex process of sex

assignment. Parental wishes and cultural beliefs also play a role in clinical decision making.

Adolescence is a difficult time even for children without OT-DSD. Psychologists can give adolescents with this condition, the opportunity to discuss their thoughts about gender identity, sexuality, sexual orientation, and relationships in a safe and nurturing environment. In our case, MD was reared as a girl. However, her mental impairment proved that this was not as important an issue to her and her family.

Some people with 45XO/46,XY have reduced fertility however, reports have shown that patients with ovotestis have fertility potentials. About 38% of the OT-DSD patients menstruate by age 14 years after removal of testicular tissues. Ovulation and successful childbearing have also been described.

Individuals with OT-DSD may have physical features not typical of a normal individual. This poses stigma hence, social isolation. Peer support ends these problems. Support groups can help families and patients find the best quality care they need.

Lastly, and most apparent in our patient, is the risk of malignancy. Germ cell tumors, especially dysgerminomas, in patients with OT-DSD, ranges from 4% to 10% Other tumors include gonadoblastoma, seminoma, cystadenoma and Sertoli-cell-tumour. Teratoma, nephroblastoma and thecoma were reported once. Our patient had endodermal sinus tumor, a germ cell tumor not usually associated with OT-DSD, but considered highly malignant.

F. Treatment

Most treatments involve some combination of surgery and chemotherapy. Treatment with cisplatin, etoposide, and bleomycin has been described. Before modern chemotherapy, this type of neoplasm was highly lethal, but the prognosis has significantly improved since. When treated promptly with surgery and chemotherapy, death from endodermal sinus tumors is exceedingly rare. Unfortunately, our patient was not able to undergo chemotherapy. Aside from the inability of the parents to pay for the cost of the treatment, patient, first and foremost, was not a good candidate to receive such a treatment. She was not medically fit because of the other health problems that she developed including persistent hypokalemia (due to secondary hyperaldosteronism), protein-energy malnutrition and urosepsis. Furthermore, the cancer cells have spread to other distant organs including the liver, as seen intra-operatively. Patient's prognosis was explained to the parents by doctors who took care of her and they decided not to pursue with the treatment and bring the patient home where they believe she could rest more.

SUMMARY AND CONCLUSION

We are presented with a 14 year-old, nulligravid, who came in at our institution with an 8-week history of abdominal enlargement and weight loss. She also had ambiguous external genitalia, primary amenorrhea, delayed secondary sexual characteristics and other phenotypic features of Thurner Syndrome. She underwent exploratory laparotomy revealing an infantile uterus, gonadal streak and contralateral gonadal tumor which on histopathology revealed an endodermal sinus tumor with both female (fallopian tube) and male (rete testis and epipidymis) reproductive tissues seen on one slide. This finding of a possible true hermaphroditism in our patient became more interesting when chromosome analysis revealed a 45 XO/46 XY karyotype. Malignant degeneration of ovotestis, commonly into gonadoblastoma, seminoma and dysgerminoma is common but is unusual to develop into endodermal sinus tumor as in our patient. Immediate detection of condition of OT-DSD is very crucial to prevent malignant degeneration or institute immediate therapy to those affected. Rearing and fertility issues are also present. Genetic and psychosocial counseling is also of prime importance in cases of genetically-challenged individuals. Mosaicism or chimerism as a cause of true hermaphroditism (now termed as Ovotesticular Disorder of Sexual Development (OT-DSD) will forever be a mystery since this can only be differentiated through embryology, a mosaic being with different types of cells arising from the same fertilized egg, whereas a chimera comes from more than one.

REFERENCES

1. Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants: Incidence of chromosome abnormalities. *Clin Genet*. 1975; 8:223-43.[PubMed]

2. Krob G, Braun A, Kuhnle U. True hermaphroditism: Geographical distribution, clinical findings, chromosomes and gonadal histology. *Eur J Pediatr.* 1994;153:2-10.[PubMed]

3. Damiani D, Fellous M, McElreavey K, Barbaux S, Barreto ES, Dichtchekenian V, et al. True hermaphroditism: Clinical aspects and molecular studies in 16 cases. *Eur J Endocrinol*. 1997; 136:201-4. [PubMed]

4. John CA, Hughes IA. Disorders of sex development. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. *Williams Textbook of Endocrinology*. 11th edition. WB Saunders; 2008. pp. 783-848.

5. Aaronson IA. True hermaphroditism: A review of 41 cases with observations on testicular histology and function. *Br J Urol*. 1985; 57:775-9. [PubMed]

6. Schultz BA, Roberts S, Rodgers A, Ataya K. Pregnancy in true hermaphrodites and all male offspring to date. *Obstet Gynecol*. 2009;113:534-6. [PubMed]

7. *Indian J Endocrinol Metab*. 2012 Jul-Aug; 16(4):640-642.

8. Vern L. Katz, MD, et al. Comprehensive Gynecology 5th edition. 2007.

9. www.wikipedia.org/wiki/True_hermaphroditism

10. Joe Leigh Simpson, MD, Ernst W. Bertner Chairman and Professor, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas (Vol 2, Chap 98; Vol 3, Chaps 69, 112; Vol 4, Chap 66; Vol 5, Chaps 79, 80, 84, 86, 87, 90; Vol 6, Chap 37) Chapter 38. True Hermaphroditism. Available from: http://www.glowm.com/resources/glowm/cd/pages/v5/v5c084.html

11. 11 True Hermaphroditism and Mixed Gonadal Dysgenesis in Young Children: A Clinicopathologic Study of 10 Cases. Kyu-Rae Kim, M.D., Youngmee Kwon, M.D., Jae Young Joung, M.D., Kun Suk Kim, M.D., Alberto G. Ayala, M.D., Jae Y. Ro, M.D.Departments of Pathology (K-RK, YK, JYR) and Urology (JYJ, KSK), University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; and Department of Pathology (AA), The University of Texas, M.D. Anderson Cancer Center, Houston, Texas. *Mod Pathol* 2002; 15(10):1013-1019

12. Kalum T. Wettasinghe1, Nirmala D. Sirisena1, Prabha H. Andraweera1, Rohan W. Jayasekara1, and Vajira H. W. Dissanayake. A Case Series of Five Sri Lankan Patients with Ovotesticular Disorder of Sex Development. *Clin Pediatr Endocrinol* 2012; 21(4):69-73.

13. 13 45,X/46,XY Mosaicism: Report of 27 Cases by Chaussain Louise Telvi, Aziza Lebbar, Olivia Del Pino, Jacques Patrick Barbet and Jean Louis. *Pediatrics* 1999; 104:304

14. http://en.wikipedia.org/wiki/Chimera_(genetics)

15. http://en.wikipedia.org/wiki/Endodermal_sinus_tumor

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