A case report on ovotesticular disorder of sexual development 46, XY with malignant mixed germ cell tumor (yolk sac tumor, dysgerminoma, mature cystic teratoma)

By Tessa Mae J. Bonguyan, MD and Darleen SJ. Estuart, MD, FPOGS
Department of Obstetrics and Gynecology, Brokenshire Memorial Hospital

ABSTRACT

This paper reports a case of a 19 year-old born with ambiguous genitalia, who presented with abdominopelvic mass diagnosed to have Ovotesticular Disorder of Sexual Development (OT-DSD) 46, XY with Malignant Mixed Germ Cell Tumor (Yolk Sac Tumor, Dysgerminoma, Mature Cystic Teratoma,). She underwent two surgeries and had gone through six cycles of Vincristine, Dactinomycin and Cyclophosphamide chemotherapy.

OT-DSD is a rare condition by the presence of both histologically proven testis and ovary in the same individual. The report describes the clinical, biochemical, imaging, and histopathologic findings and outcomes of OT-DSD complicated with gonadal tumor. Diagnostic work up, pre-operative preparations, intra operative management, post-operative follow up and chemotherapy along with psychiatric support for gender identity and assignment are discussed. This paper emphasizes the importance of multidisciplinary effort from the different fields of medicine namely reproductive endocrinology, gynecologic oncology, surgery, psychiatry, and anesthesiology.

Keywords: 46, XY disorders of sex development, disorders of sexual development, neoplasms, germ cell and embryonal, ovotesticular disorder of sexual development

INTRODUCTION

Disorders of sexual development pertain to conditions of incomplete or disordered genital or gonadal development leading to a discordance between genetic sex and phenotypic sex [8]. These are rare conditions which occur in 1:4,500 to 1:5,000 livebirths [17,19]. Ovotesticular disorder of sexual development (OT-DSD) previously known as True Hermaphroditism occurs in fewer than ten percent of all disorders of sexual development [9]. OT-DSD, 46, XY karyotype occurred most infrequently. Krob et al, reviewed 283 cases of true hermaphrodites reported in the literature between 1980 to 1992, and found that 46, XX occurred most frequently (71%), followed by mosaicism, usually 46 XX/46 XY (20%) and 46, XY (7%). More than five hundred cases of OT-DSD including familial cases have been reported[11]. In Davao City, Philippines, this is the second reported case of OT-DSD [12].

The frequency of gonadal tumors in patients with OT- DSD has been reported as 2.6-4.6% [11, 20]. Patients with 46, XY and 46, XX/XY OT-DSD tend to develop gonadal tumors more commonly than those with 46, XX karyotype. Tumors have been described in both ovarian and testicular portions. The incidence of gonadal tumors increases with age in disorders of sexual development patients with the Y chromosome. This patient was diagnosed to have Malignant Mixed Germ Cell Tumor, Right Ovotestis (Yolk Sac Tumor, Dysgerminoma, and Mature Teratoma) Stage IA.

This case is reported because of its rarity and complexity that posed a diagnostic and management challenge.

CASE REPORT

J.T., 19 years-old, single, from Davao City was admitted due to abdominal pain.

The patient was delivered vaginally with ambiguous genitalia.

She was raised as female with developmental milestones at par with age. Linear growth was rapid at 12 years-old, thelarche and pubarche at 13 years-old. Her peak growth velocity was at 17 to 18 years-old. She never had menses.

She identifies herself as a female who is attracted to females. In 2nd grade, she wore dresses. At age 10, she was boyish and liked to play with boys, she also noticed that she can run as fast as her boy pals. At age 12, though she had male crushes, she started to feel attracted to females. She started dating at 17 years-old and she is currently in a relationship with another female. She never had sexual contact. J.T. is a member of a women's basketball

*2nd Place, 2016 Philippine Obstetrical and Gynecological Society (POGS) Midyear Interesting Case Paper Contest, July 05, 2016, Grand Ballroom B & C, Marriott Hotel, Resort Drive, Pasay City

varsity team which granted her college scholarship. She is currently a 2nd year college student in Human Resource Management.

Four months prior to admission, she noted gradually enlarging abdomen and gnawing abdominal pain. Ultrasound revealed pelvo-abdominal solid-cystic mass measuring 22.12 x 23.65 x 9.50 cm with Sassone 13. Uterine corpus and cervix were absent. Both ovaries were not identified with moderate free fluid in the cul de sac. Cancer antigen (CA) 125 was slightly elevated.

Magnetic resonance imaging (MRI) showed a large abdominopelvic mass, right, with mesenteric lymphadenopathy, consider a Malignant Germ Cell Tumor, undescended testis, right inguinal region. Karyotyping was not done at this time due to cost constraints. Chromatin Barr bodies was positive. Estradiol level was low. Testosterone, leutinizing hormone (LH), follicle stimulating hormone (FSH), lactate dehydrogenase (LDH), beta human chorionic gonadotropin (B-hCG) and alpha feto protein (AFP) were all high, free thyroxine (FT4), thyroid stimulating hormone (TSH) and dehydroepiandrosterone (DHEAS), complete blood count, serum electrolytes, serum creatinine and urinalysis were all within normal limits (Table1).

The impression was probable Malignant Germ Cell Tumor, Partial Androgen Insensitivity Syndrome (PAIS), G0. The patient and her family underwent counseling.

The patient is 5'6' tall and weighs 51 kg (Figure 1A). She had sparse hair on her upper lip. No anterior neck mass or any neck prominence were noted. Her breasts were symmetrical with breast budding at Tanner Stage II without discolorations, retractions, tenderness or nipple discharge (Figure 1B). Fine, sparse, axillary hair were noted (Figure 1C). Her abdomen was globular, with a soft, tender, movable, abdominopelvic mass measuring 21 x 16 cm up to the level of the umbilicus. The pubic hair was adult in type and quantity with spread to the medial thigh at Tanner Stage IV (Figure 2C). A phallus, labia majora and minora, urethral opening and vaginal opening were noted. The micropenis phallus measured 4.5 x 2 cm with no urethral opening (Figure 2A). The urethral opening was located at the lower third of the perineum (Figure 2B). The vagina with intact hymen was located just below the urethra (Figure 2B).

She underwent exploratory laparotomy, peritoneal fluid sampling, omentectomy, right salpingo oophorectomy, enterolysis, adhesiolysis and chromotubation. A grossly normal corpus and left adnexa were seen. The right fallopian tube was twisted twice. The right ovary was a complex mass measuring 30 x 17 x 9 cm occupying the abdominopelvic cavity (Figure 3). Frozen section biopsy revealed Yolk Sac tumor. The post-operative diagnosis was Yolk Sac Tumor, Right Ovary, by frozen section biopsy, Stage IA; Ovarian Torsion, right; pending histopathologic

Table 1

Laboratory Tests	Patient's Result	Normal Values
Estradiol	5.00 pg/ml	Men: 7.63- 42.69 pg/ml Women: Follicular: 12.53- 165.5 Ovulatory: 85.78- 498 Luteal: 43.8- 211 Postmenopause: < 5- 54.72
Testosterone	1.46 ng/ml	0.06 - 0.82 ng/ml
FSH	98.81 mIU/ml	Men: 1.5- 12.4 mIU/ml Women: Follicular: 3.5 -12.5 mIU/ml Ovulatory: 4.7 - 21.5 Luteal: 1.7-7.7 Postmenopause: 25.8-134.8
LH	62.92 mIU/ml	Men: 1.7- 8.6 mIU/ml Women: Follicular: 2.4-12.6 Ovulatory: 12- 95.6 Luteal: 1..0 - 11.4 Postmenopause: 7.7 -58.5
LDH	264 U/L	135-214 U/L
BHCG	369mIu/ml	<1 mIu/ml
AFP	>3000 ng/ml	0-9 ng/ml
FT4	1.22 ng/dl	0.58-1.64 ng/dl
TSH	2.28uIu/ml	0.34- 5.60 uIu/ml
DHEAS	3 ug/dl	145- 395 ug/dl
s. creatinine	58 mg/dl	0.60-1.3 mg/dl
CA-125	51.5 U/mL	0-35 u/mL

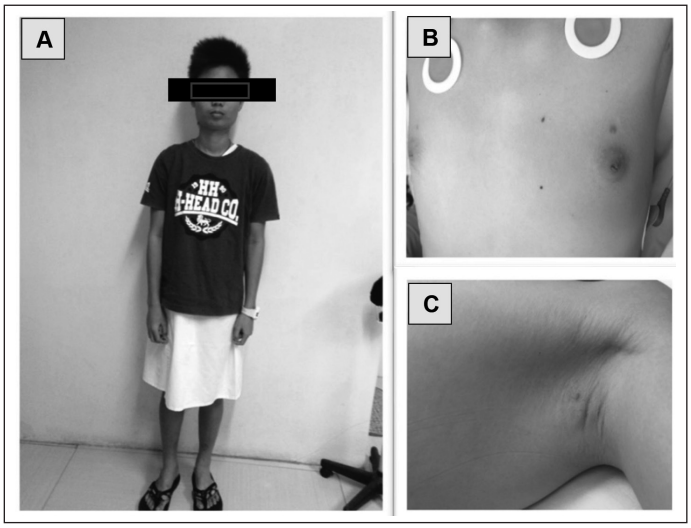

Figure 1A: Gross appearance of the patient
Figure 1B: Breasts were symmetrical and with elevation of breasts and papilla and enlargement of the areola
Figure 1C: Minimal growth of axillary hair

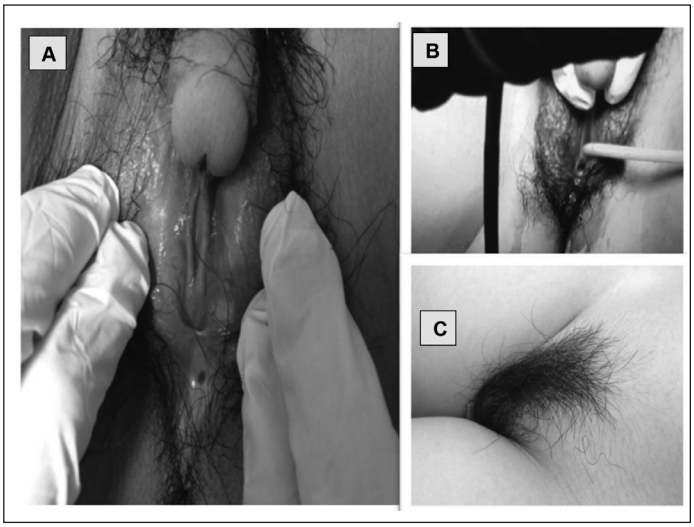

Figure 2A: Closer view of the phallus of the micropenis with no urethral opening and perineum with labia minora and majora
Figure 2B: Closer view of the urethral meatus locate at the lower third of the vestibule above the vagina
Figure 2C: Closer view of the pubic hair with female distribution extending across the pubis but sparing the thighs

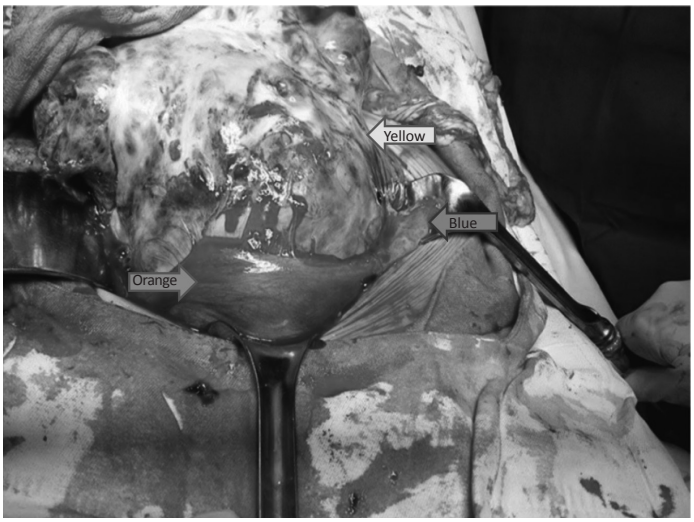

Figure 3. The yellow arrow shows a complex right adnexal mass; the blue arrow shows a grossly normal left adnexa; the orange arrow shows a small uterus.

report, G0. PAIS was ruled out because of the presence of the uterus and adnexa.

Hemoglobin was 10.2 g/dl and serum testosterone was low at < .025 ng/ml. She was discharged improved.

Biopsy showed: Malignant mixed germ cell tumor (Yolk sac tumor, Dysgerminoma, Mature Cystic Teratoma), fallopian tube, seminiferous tubules, presence of follicles (Figure 4). No atypical cells seen on cell cytology.

The patient and her family were apprised of the type of tumor, the proposed management and the prognosis of her condition. It was emphasized that chemotherapy should be started after 1-2 weeks. The family was hesitant to start chemotherapy, hence, there was a delay.

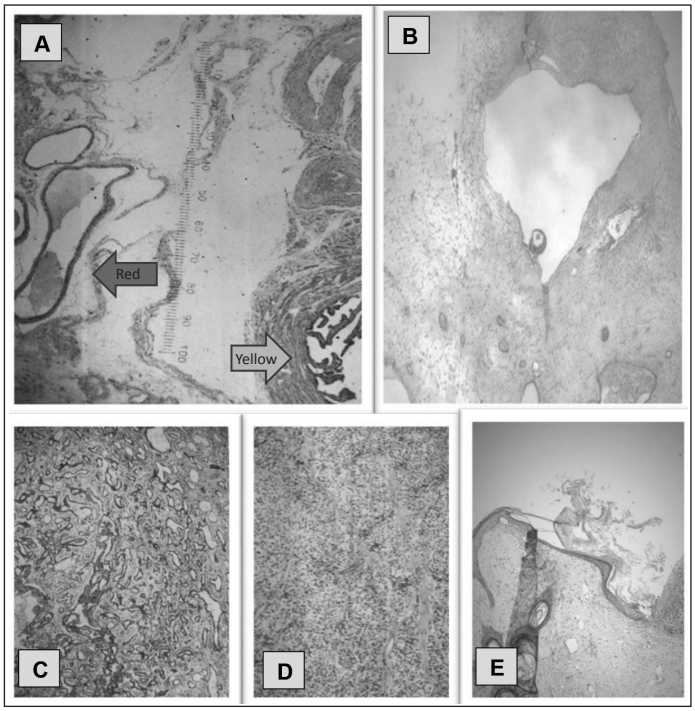

Figure 4. Biopsy findings of the right adnexal mass show: (A) red arrow: presence of seminiferous tubules, yellow arrow: presence of fallopian tube (B) presence of an ovarian follicle (C) tumor cells in loose reticular pattern of a Yolk Sac tumor (D) incomplete lobules with uniform small cells with clear cytoplasm of a Dysgerminoma (E) hair bulb and follicle of a Mature Cystic Teratoma

Moreover, the presence of the both seminiferous tubules and ovarian follicle in the same mass raised the dilemma of the genetic sex of the patient, which karyotyping could answer. This test was followed up.

Three (3) weeks post operatively, chromosomal analysis revealed male karyotype of 46 chromosomes, confirmed by gross G banding. Repeat serum AFP was elevated at 3274 iu/l. The importance to start chemotherapy was re-emphasized and the patient and her immediate family underwent genetic counseling.

Upon knowing the karyotype result, the working impression was challenged. The patient had ambiguous genitalia with non palpable gonads, 46, XY karyotype, with the presence of uterus, and ovotestis, three disorders of sexual development were considered: Mixed gonadal dysgenesis, Swyer's syndrome and Ovotesticular disorder of sexual development (OT- DSD).

The former two were ruled out because only OT-DSD could have a histopathologic result of an ovarian follicle with seminiferous tubules in the same mass. Hence, the final diagnosis was Mixed Germ Cell Tumor (Yolk Sac tumor, Dysgerminoma, Mature Cystic Teratoma), Torsion of Right Ovotestis, Stage IA, OT-DSD (46, XY).

Eight (8) weeks post operatively, the patient complained of persistent lumbar pain. She also noticed a

gradually enlarging abdominal mass. Serum AFP B-hCG, and CA-125 were high while her carcino embryonic antigen (CEA), urinalysis, and complete blood count were within normal limits (Table 2). Transrectal, transabdominal ultrasound and MRI showed abdominal Mass, consider tumor recurrence, left hemipelvis with large metastatic para aortic lymphadenopathy.

Twelve (12) weeks after the first surgery, she underwent exploratory laparotomy, peritoneal fluid sampling, and total abdominal hysterectomy with left salpingo-oophorectomy, extensive adhesiolysis, and tumor debulking of para aortic mass. The liver had nodularities, multiple seedings were seen on the omentum, intestines and posterior and anterior cul de sac, the uterus was infantile and left fallopian tube and ovary looked grossly normal. A solid mesenteric mass was noted at the midline posterior to and covered by the intestines. It was fixed, friable and measured 14 x 10 cm (Figure 5). Post-operative diagnosis was Malignant Mixed Germ Cell Tumor (Yolk sac tumor, Dysgerminoma, Mature Cystic Teratoma) Stage IA, Right Ovotestis; Tumor Recurrence with Progression (Left Ovary, Paraaortic Mass).

Histopathologic result revealed yolk sac tumor of the left ovary and paraaorta; uterus and left fallopian tube.

Six (6) weeks after her second surgery, the patient had her first cycle of chemotherapy with Vincristine, Dactinomycin and Cyclophosphamide.

Currently, she already finished 6 cycles of chemotherapy. She is back to school and rejoined her basketball team as an observer.

DISCUSSION

In this case, three disorders of sexual development were deliberated: Swyer's syndrome, Mixed Gonadal Dysgenesis and Ovotesticular- Disorder of Sexual Development (OT-DSD).

Table 2

Laboratory Tests	Patient's Result	Normal Values
AFP	> 3000 ng/ml	0-9 ng/ml
B-hCG	1265.17 mIu/ml	< 1 mIu/ml
CA-125	42.6 u/mL	0-35 u/mL
CEA	0.66 ng/L	0-10 ng/L
Hemoglobin	12.1 g/dL	12.0-16 .0 g/dL
Platelelet	331	150-400 x 10 9/L
WBC	8.3	4-10.0 x 10 9/L
Neutrophils	0.74	0.55-0.65 g/L

Swyer's syndrome or XY gonadal dysgenesis manifests as bilateral dysgenetic gonads with underdeveloped Mullerian derivatives[7]. This was considered since the patient's karyotype was 46, XY and she presented with underdeveloped breasts, axillary and pubic hair with female distribution, small uterus and gonadal tumor. However, this was ruled out since the patient had genital ambiguity and histologic finding of a right ovotestis.

Another condition considered was Mixed Gonadal Dysgenesis, defined as presence of testis on one side and a streak gonad on the other[7]. This was considered since patients with this condition have a male karyotype. They also present with ambiguous genitalia, gonadal tumor, a rudimentary uterus and fallopian tube, presence of seminiferous tubules in the mass and elevated serum gonadotropin levels. However, this condition was ruled out since the contralateral gonad is not streaked and the histologic finding of an ovotestis confirmed that, indeed, she has OT-DSD. In this case, the patient decided to keep her female gender identity despite knowing that she had a male karyotype.

OT-DSD refers to a rare condition in which well-defined ovarian tissues occur along with well-defined testicular tissues in the same individual [18].

The gonads may be ovotestis, or they may be a combination of an ovary on one side and a testis or ovotestis on the other. According to a review on gonadal distribution of 409 true hermaphrodites by Niekerk et al, ovotestis is the most common gonad. It was found in 44.3%, an ovary on the left side of the body in 62.8% and testis on the right side in 59.5%. In this case, the right gonad is an ovotestis and the left gonad is an ovary, both in the ovarian location. Ovaries and ovarian portions of ovotestis may appear normal with follicular growth and estradiol production which may have been the case of the patient since both gonads' histopathology result showed some ovarian follicles and hyalinized seminiferous tubules with poor germ cell development and Tanner II breast development [20].

The clinical presentation of OT-DSD vary to some extent depending on the patient's age at the time of diagnosis [1, 8]. Despite the fact that most people with OT-DSD present with genital ambiguity, less than twenty percent are diagnosed before 5 years-old. Seventy-five percent are diagnosed by age 20 years. For gender assignment, in a series of van Niekerk et al, 73% of patients with OT-DSD were raised as males and 27% as females. This patient was identified to have genital ambiguity at birth, however, no diagnostic work up or laboratory exams were done. [20]

Because of functioning normal ovarian tissue, most people affected with OT-DSD have breast development at puberty which is present in our patient. It was also

recorded that 50% of those with OT-DSD karyotype 46, XX menstruate during puberty which is not present in this case. Aside from the physical and emotional consequences associated with genital ambiguity, patients with OT-DSD usually possess average intelligence and in general have a normal life expectancy.

Diagnostic tests that are recommended for patients with genital ambiguity and primary amenorrhea are the following: karyotyping, Fluorescence in situ hybridization (FISH), serum 17 hydroxyprogesterone, testosterone, FSH, LH, DHEAS, estradiol, anti mullerian hormone, serum electrolytes, adrenocorticotropic hormone (ACTH), cortisol, and ultrasound of the pelvis and abdomen (Speroff, chapter on amenorrhea). All were done except 17 hydroxyprogesterone, ACTH, and anti mullerian hormone test since these tests were locally unavailable and costly if done elsewhere.

An aspect of OT-DSD that is difficult to manage is choosing the ideal gender when faced with an ambiguous genitalia. There is the risk that childhood and adolescence for affected individuals will be compromised by gender identity disorder and other psychosexual problems, which may carry over into adult life [2, 14]. For J.T., she still considers herself a homosexual female with a male karyotype.

The presentation and management of DSD in different cultures, poverty seems to be the main factor affecting long term outcome as it denies the patient access to early diagnosis [10].

Germ cell tumors consist of 70% of all ovarian tumors in children and adolescents. Germ cell tumors are derived from the primordial germ cells of the ovary or testis. The majority of germ cell tumors arise in the gonad from the undifferentiated germ cells. Mixed germ cell tumor consists 8.6% of ovarian malignancies in children or adolescent. The yolk sac tumor is seen in 88% of mixed germ cell tumor [4].

Malignant germ cell tumor (MGCT) of ovary is almost always unilateral at diagnosis. In about 10% of tumors the mass may grow rapidly, resulting in acute abdomen due to capsular distension, necrosis, hemorrhage, rupture or torsion [22]. All these were present in the patient.

Prior to the first surgery, all tumor markers were elevated. All other laboratory examination results of this patient were normal.

The aim of the primary surgery was to remove the primary tumor causing the patient's abdominal pain, to get an accurate histological diagnosis and to assess the disease extent. Biopsy of the gonads for histologic confirmation and removal of intra-abdominal testis or streak gonads with Y chromosome-DNA is recommended since this has high malignant potential. Moreover, it is only prudent to remove all wolffian structures and testicular tissue if the patient has been given a female gender assignment and removal of müllerian structures and ovarian tissue if the patient has been given a male gender assignment [6]. Second look surgery was performed in this case to complete surgical treatment and for tumor debulking.

Surveillance is an important component of the management in Malignant Germ Cell Tumors, hence, tumor marker and imaging studies are taken serially and done post operatively. The patient had elevated AFP which was taken 4 weeks post operatively after her first surgery which implied the rapid progression of the tumor [5, 22]. It was reemphasized that a second look surgery must be done and it is important to start chemotherapy immediately after surgery.

Chemotherapy given was vincristine 1.5mg/m2 given intravenously weekly for 12 weeks and actinomyin D 0.5 mg and with cyclophosphamide 5 to 7 mg/kg/day given intravenously for 5 days for 4 weeks.

SUMMARY

OT-DSD should be considered as one of the differential diagnoses in young adults with genital ambiguity, non-palpable gonads, underdeveloped breasts, and abdominopelvic mass. Delayed diagnosis leads to clinical and psychological problems and increased risk of neoplasia which happened in this case.

A holistic multidisciplinary team management, with professional mental health support for patients and families, patient-centered and evidence based process for decision making, expertly performed surgery, optimal hormonal management and close tracking of patients and families are advocated.

J.T., not only struggled with chemotherapy and cancer but also with her gender identity. Identity and self-esteem issues in this age group make psychological and family support of utmost importance. She is blessed to have parents and basketball teammates who love and support her in this battle. ■

REFERENCES

1. Ahmed SF, Achermann JC, Arlt W, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. *Clinical Endocrinology (Oxf.)* 2011; 75:12-26.

2. Ahmed SF, Auchus R, Baratz A, Baratz D, Houk CP, Lee PA, Liao LM et al. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. *Horm Res Pediatrics* 2016; 85 (3):158-160.

3. Allen J, Brecher M, Cooney D, Fisher J, Green D, Grossi M. The Use of Different Induction and Maintenance Chemotherapy Regimens for the Treatment of Advance Yolk Sac Tumors. American Society of Clinical Oncology 1983.

4. Breen, J, Denehy, T, Taylor R, Glob. libr. women's med.,(ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10251.

5. Coleman R, Ramirez P, Gershenson D. Neoplastic Diseases of the Ovary. In: Lentz G., Lobo R, Gershenson D, Katz V (eds): Comprehensive Gynecology. Elsevier Health, 2012; 32.

6. Donahoe, P. Pieretti R. Surgical Treatment of Disorders of Sexual Development. In:Coran A, Spitz A (eds): Operative Pediatric Surgery. USA: CRC Press, 7th ed. USA: 2013; 946.

7. Fritz, M, Speroff L (eds): Clinical Gynecologic Endocrinology and Infertility. 8th Edition. USA: Lippincot Williams and Wilkins. 346-387.

8. Houk CP, Lee PA 2005 Intersexed states: diagnosis and management. *Endocrinol Metab Clin North Am* 34:791-810.

9. Josso N, Audi L, Shaw G. Regional variations in the management of testicular or ovotesticular disorders of sex development. *Sex Dev.* 2011; 5(5):225-34.

10. Julka S, Bhatia V, Singh U, Northam E, Dabadghao P, Phadke S,et al. Quality of life, gender role and timing of surgery in disordersof sexual differentiation in India. *J Pediatr Endocrinol Metab* 2006; 19:879-88.

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

12. Luy S, Ho F. A Rare Case of True Hermaphrodite with Features of Klinefelter Syndrome. *Philippine Journal of Internal Medicine* 2013; 51(4):6-8.

13. Mongan NP, Tadokoro-Cuccaro R, Bunch T, Hughes IA. Androgen insensitivity syndrome. *Best Pract Res Clin Endocrinol Metab*. 2015 Aug. 29; (4):569-80.

14. Pasterski V, Prentice P, Hughes IA. Consequences of the Chicago consensus on disorders of sex development (DSD): current practices in Europe. *Arch Dis Child*. 2010; 95(8):618-623.

15. Pleskacova J, Hersmus R, Oosterhuis JW, Setyawati BA, Faradz SM, Cools M, Wolffenbuttel KP, Lebl J, Drop SL, Looijenga LH. *Sex Dev.* 2010 Sep; 4(4-5):259-69.

16. Powell, C. Sex Chromosome2, s and Sex Chromosome Abnormalities. In: Gersen S, Keagle M: The Principles of Clinical Cytogenetics, Totowa, New Jersey: Humana Press Co., 2005; 207-246.

17. Sax L: How common is intersex? A response to Anne Fausto-Sterling. *J Sex Res* 2002; 39:174-178.

18. Talerman A., Vang R. Kurman R. Germ Cell Tumors of the Ovary. In: Hedrick E, Ronnett, L, Brigitte M.: Blaustein's Pathology for the Female Genital Tract, USA: Springer. 2011; 16.

19. Thyen U., Lanz K., Holterhus P.M, Hiort, O. Epidemiology and initial management of ambiguous genitalia at birth in Germany. *Horm Res* 2006; 66:195-203.

20. Van Niekerk WA, Retief AE. The gonads of human true hermaphrodites. Hum. Genet. 1981; 58: 117–22. Vilain E. The genetics of ovotesticular disorders of sex development. *Adv Exp Med Biol* 2011; 707:105-6.

21. Warne GL, Bhatia V. Intersex, east and west. In: Sytsma SE, editor. Ethics and intersex. New York: Springer. 2006; 183-205.

22. Werner C, Moschos, E, Griffith W, Beshay V, Rahn, D, Richardson D. (eds):Williams Gynecology, 2nd ed. USA: Lippincot Williams & Wilkins, 2012.