Mixed Gonadal Dysgenesis (45 XO/46 XY Mosaicism): A Case Report

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Disorders of sexual development (DSD) defined as congenital conditions associated with atypical development of anatomical, gonadal or chromosomal sex, is a rare condition that may present with ambiguous genitalia. Included in the varied classes of DSD is mixed gonadal dysgenesis which is known to be due to mosaicism, a chromosomal aberration. Mosaic individuals may have concerns on growth, hormone balance, gonadal development, sex of rearing and fertility. This case report presents an 18-year old student who presented with primary amenorrhea, delayed secondary sexual characteristics and phenotypic features of Turner syndrome who, on chromosomal analysis revealed 45XO/46XY mosaicism. The patient underwent operative laparoscopy with bilateral gonadectomy on the basis of the increased risk of development of gonadal malignancy in phenotypic females with Y-chromosome material. Histopathological analysis revealed bilateral streak gonads. Hormone replacement therapy was then initiated for the induction of secondary female sex characteristics, as treatment for estrogen deficiency, for the induction of pubertal growth spurt and for optimization of bone mineral accumulation. Management of disorders of sexual development is challenging, thus the need for a multidisciplinary approach involving experts in endocrinology, gynecology, psychology and genetics.

Key words: Mixed gonadal dysgenesis, mosaicism, Turner syndrome, gonadectomy

Introduction

The disorders of sexual development (DSD), previously referred to as intersex disorders, are uncommon disorders with an incidence of 1:4,500 to 1:5,000 live births.[1] They comprise a variety of congenital diseases with anomalies of the sex chromosome, gonads, reproductive ducts and genitalia. DSD is loosely classified into four groups on the basis of histological features of the gonadal tissue: XX-DSD with two ovaries (female pseudohermaphroditism), XY-DSD with two testicles (male pseudohermaphroditism), ovotesticular DSD with both ovarian and testicular tissue (true hermaphroditism) and gonadal dysgenesis.[2]

Gonadal dysgenesis is a kind of disorder in which the development of the indifferent embryonic gonad to differentiated gonads is inhibited. The group includes pure gonadal dysgenesis (46, XX or 46, XY = Swyer syndrome), mixed gonadal dysgene is (mosaic 45,X0/46,XY etc.) and Turner syndrome. The gonads are usually hypoplastic and dysfunctional with a complete germ cell deficiency.[3,4,5]

Mixed gonadal dysgenesi (45,X0/46,XY) is caused by chromosomal mosaicism with heterogeneous clinical picture because the endocrine function of the testes can be affected in various degrees. The external genitalia can have a phenotype ranging from female to male, although in most cases, the genitalia are intersexual with hypertrophy of the clitoris or hypospadias.[6]

Dysgenetic testes have a high risk for malignancy and can develop into malignant germ cell tumors such as dysgerminomas or gonadoblastomas.[7,8,9] as the existence of the GBY region on the Y chromosome as well as the testes specific protein gene (TSPY) on the Y chromosome predispose for a malignant transformation.[7] In contrast, dysgenetic ovaries do not seem to have increased risk for malignancy. The risk of gonadoblastoma is more common in cases of gonadal dysgenetic syndromes as compared to true hermaphrodites (15% to 35% vs. 0.2% to 0.4%).[10,11]

As a preventive measure, bilateral gonadectomy is recommended.[3,12] In females with mixed gonadal dysgenesis, although tumor risk is limited, gonads are not functional, making gonadectomy the most reasonable option.[13]

Detailed physical examination and step-wise investigations including genetic testing, hormonal evaluation and imaging studies are strongly recommended to establish the diagnosis of mixed gonadal dysgenesis.[14] Various factors including proper 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 surgical management.[15]

This is a case report about a patient who presented with classic manifestations of mixed gonadal dysgenesis, and how a comprehensive, holistic, and step-wise investigation and management helped the patient and her family accept the diagnosis.

The Case

This is a case of M.P., an 18 year old nulligravid, single, reared as a female, who consulted due to primary amenorrhea. The patient has no comorbidities, hospitalizations nor allergy to food and drugs. The patient's mother has hypertension while her father has bronchial asthma. There are no other familial diseases such as diabetes, heart disease or history of developmental delay in the family.

The patient is a college student (Bachelor of Science in Education) who is consistently on top of her class. She has no vices and has had no coitus yet. She is living with her parents and four cousins. Her father is a carpenter while her mother runs a small family-owned store.

While pregnant, the patient's mother had regular prenatal check-ups with intake of folic acid, multivitamins and ferrous sulfate. Her mother had an unremarkable 1st and 2nd trimester prenatal course. At 30 weeks age of gestation, patient's mother presented with elevated blood pressure and eclampsia, prompting an emergency preterm delivery via cesarean section. The patient remained at the neonatal intensive care unit for two weeks due to prematurity but was later discharged. The patient's genitalia was noted to be that of a normal baby girl and she was assigned a female gender. The patient was given complete immunization including MMR, hepatitis, polio and diphtheria.

The patient's developmental milestones were at par with age, until at 10 years old, when her mother noticed a slow increase in the patient's height compared to other children her age. No consult was done since there were no other developmental delays noted. In fact, she was a consistent honor student from grade school until high school. However, now at 18 years old, patient still has no menses, nor development of other secondary sexual characteristics. This prompted consult to PGH.

Review of systems was unremarkable. The patient was conscious, coherent, ambulatory and not in cardiorespiratory distress. She had stable vital signs. She displayed physical features characteristic of Turner syndrome, i.e. short stature (134 cm) with weight of 35.5 kg and BMI of 19.74 kg/m^2, short neck, wide-spaced nipple, shield-shape chest and cubitus valgus (Figure 1). She also has thoracolumbar scoliosis (Figure 2). She had Tanner Stage 1 breasts and pubic hair, with absent axillary hair (Figure 3). She had symmetrical chest expansion, with clear breath sounds, adynamic precordium and no murmurs were heard. The abdomen was flabby with no masses nor tenderness. She had no motor nor sensory deficits. She had normal external genitalia, intact hymen, and normal-sized clitoris. The cervix and uterus were not palpable and there was no mass palpated in the cul-de-sac. She had good sphincteric tone and intact rectal vault.

Transrectal ultrasound of the patient showed infantile uterus and streak ovaries (Figures 4 & 5). Whole abdominal ultrasound showed normal liver, gallbladder, pancreas, spleen, urinary bladder and kidneys. Echocardiogram revealed mild mitral regurgitation, tricuspid regurgitation, aortic and pulmonic regurgitation with normal pulmonary

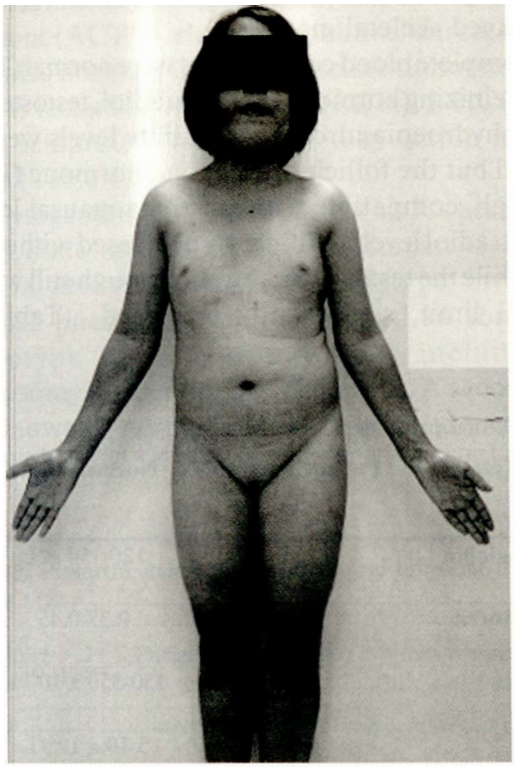

Figure 1. Patient M.P. showing physical features of Turner syndrome (short stature, short neck, wide-spaced nipple, shield-like chest, cubitus valgus).

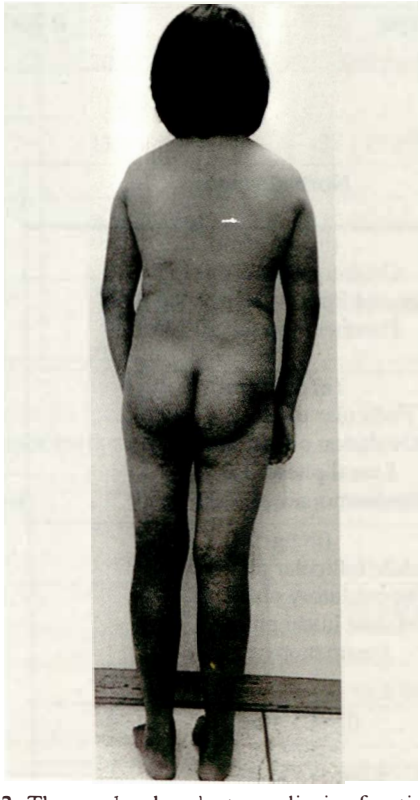

Figure 2. Thoracolumbar dextroscoliosis of patient M.P.

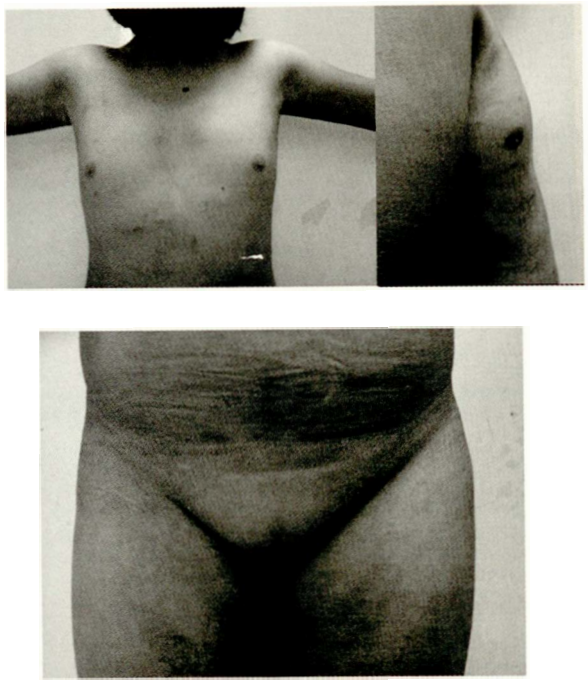

Figure 3. Delayed secondary sexual characteristics of patient M.P. showing Tanner Stage 1 for brea t and pubic hair with absent axillary hair.

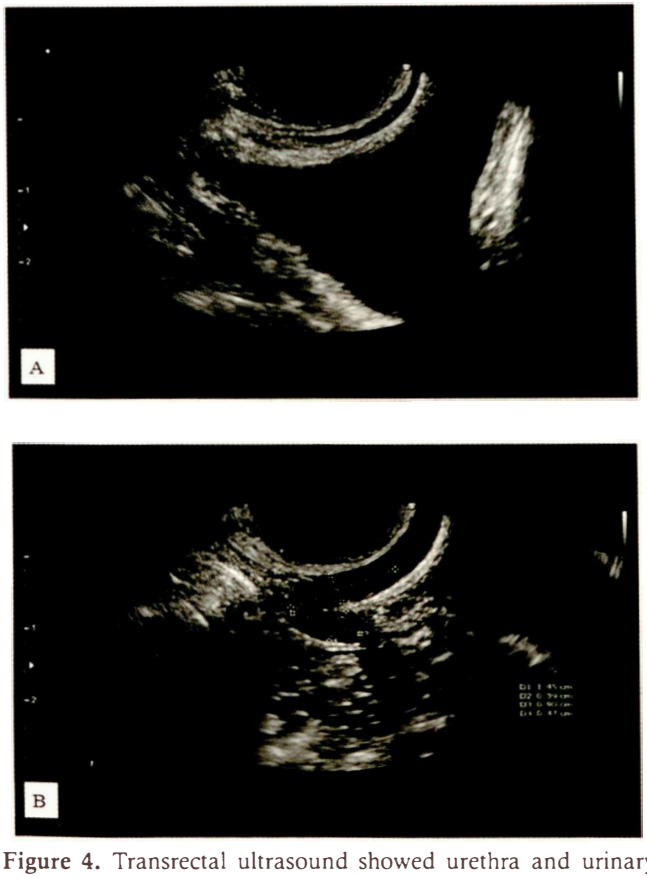

Figure 4. Transrectal ultrasound showed urethra and urinary bladder are smooth and intact but there is absent triple line sign of the vagina (A); cervix measured 1.5 cm x 0.9 cm x 0.5 cm and the anteverted uterus measured 2.4cm x 0.7cm x 0.5 cm (B).

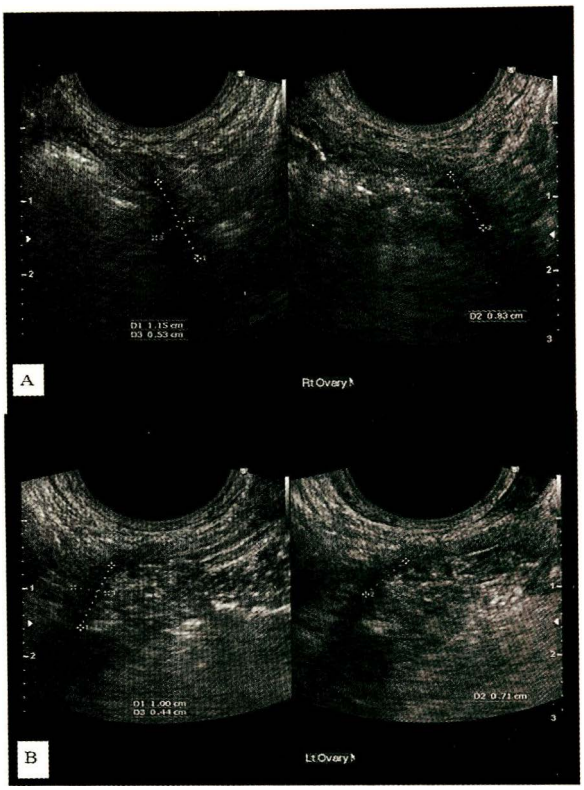

Figure 5. Patient MP's right streak gonad (A) and left streak gonad (B).

artery pressure. Bone densitometry showed bone mineral density (BMD) values below the expected range for age. Bone age (using Greulich-Pyle method) was compatible to a 16-year old female, suggestive of delayed skeletal maturity.

Complete blood count results were normal (Table 1). Luteinizing hormone (LH), estradiol, testosterone and dehydroepiandrosterone sulfate levels were all normal but the follicle stimulating hormone (FSH) was high, compatible with postmenopausal levels. The estradiol level significantly decreased within one year while the testosterone level, although still within normal limit, significantly increased (Table 2).

Table 1. Blood parameters of patient M.P.

Test	Patient's values	Normal values
Hemoglobin	135	120-150 g/L
Hematocrit	0.40	0.37-0.45
Platelet	298	150-350 x 10^9/L
WBC	4.60	5-10 x 10^2/L
Neutrophil	0.56	0.40-0.60
Eosinophil	0.06	0.01-0.06
Lymphocyte	0.38	0.20-0.40

Table 2. Gonadotrophins and sex hormone assays of patient M.P.

Test	Patient's values	Normal values
FSH	**84.75 mIU/ml**	(in mIU/ml) Ovulatory peak: 4.0-13.5 Pre and Post ovulatory: 0.6-9.5 Postmenopausal: 30-135
LH	15.2→ 17.0 mIU/ml	(in mIU/ml) Follicular phase: 2.4 – 12.6 Ovulation phase: 14.0-95.69 Luteal phase: 1.0-11.40 Postmenopausal: 7.70-58.50
Estradiol	131.3 → 86.73 pg/ml	(in pg/ml) Middle follicular phase: 57 – 227 Pre-ovulatory phase: 127-476 Middle luteal phase: 77-277 Postmenopausal: <82
Testosterone	0.97 → 2.0 nmol/L	0.9-4.5 nmol/L
DHEAS	2.7 umol/L	3.92 – 10.66 umol/L

Thyroid function test, prolactin, anti-corticotrophin hormone (ACTH), electrolytes and serum creatinine were also normal (Table 3). Baseline tumor markers such as lactate dehydrogenase (LDH), ß-HCG, and alpha fetoprotein (AFP) were also within normal limits (Table 4).

Cytogenetic analysis of patient M.P.'s peripheral blood done at the Institute of Human Genetics, Manila revealed a mosaic karyotype involving two cell lines. One cell line showed an abnormal karyotype of 45 chromosomes including a monosomy X, identified in eight cells. A second cell line showed a normal male karyotype, identified in 42 cells (i.e. 45, X [8]/46, XY [42]) (Figure 6).

Table 3. Prolactin, electrolytes and thyroid hormone assays of patient M.P.

Test	Patient's values	Normal values
TSH	2.07 uIU/ml	0.40-5.50 uIU/ml
FT4	1.27 ng/dl	0.80-2.2 ng/dl
Prolactin	9.1 ng/ml	2.6-24.8 ng/ml
ACTH	20.65 pg/ml	<40 pg/ml
Na	138 mmol/L	137-145 mmol/L
K	4.3 mmol/L	3.5 – 5.1 mmol/L
Crea	54 umol/L	46-92 umol/L

Table 4. Tumor markers of patient M.P.

Test	Patient's values	Normal values
LDH	500 IU/L	313-618 IU/L
ß-HCG	<1.2 mIU/ml	<5.0 mIU/ml
AFP	3.6 IU/ml	0.74-7.3 IU/ml

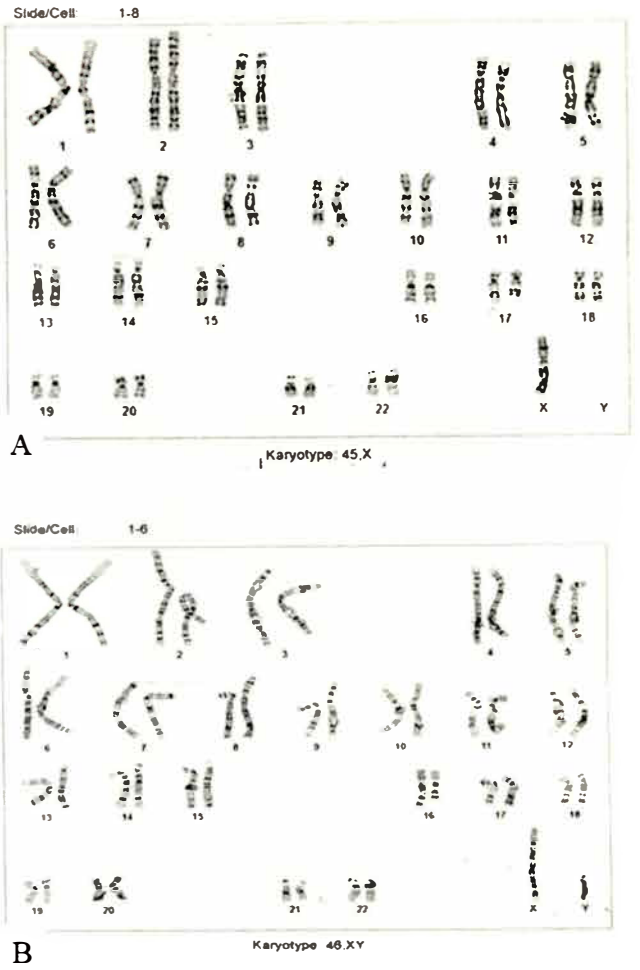

Figure 6. Cytogenetic analysis revealed a mosaic karyotype involving two cell lines. One cell line (A) showed 45, X identified in eight cells. A second cell line (B) showed a normal male karyotype, identified in 42 cells (i.e. 45, X [8]/46, XY [42]).

With the history of primary amenorrhea, delayed development of secondary sexual characteristics, physical features of Turner syndrome, imaging studies and karyotype results, the primary diagnosis on admission was Mixed gonadal dysgenesis. Due to the risk of gonadal malignancy, operative laparoscopy with bilateral gonadectomy was planned. Risks, benefits and complications of the procedure were fully explained to the patient and her family. She was referred to Psychiatry and Genetics services for counselling and appropriate clearances were secured prior to the operation.

Patient underwent operative laparoscopy under general anesthesia. Intra-operatively, the uterus was infantile, measuring approximately 1.0 cm x 1.0 cm x 1.0 cm (Figure 7a). Arising from the uterus bilaterally,

were tubular structures which seemed to be the fallopian tubes. There were bilateral streak gonads measuring approximately 2.0 cm x 1.0 cm x 1.0 cm (Figures 7b-c). Bilateral gonadectomy was done and specimens were sent for histopathology (Figure 8). Microscopic analysis revealed histologically unremarkable fallopian tubes, fibro-fatty tissues with focal ovarian-type stroma and Wolffian duct remnant which the pathologist signed out as compatible with streak ovaries.

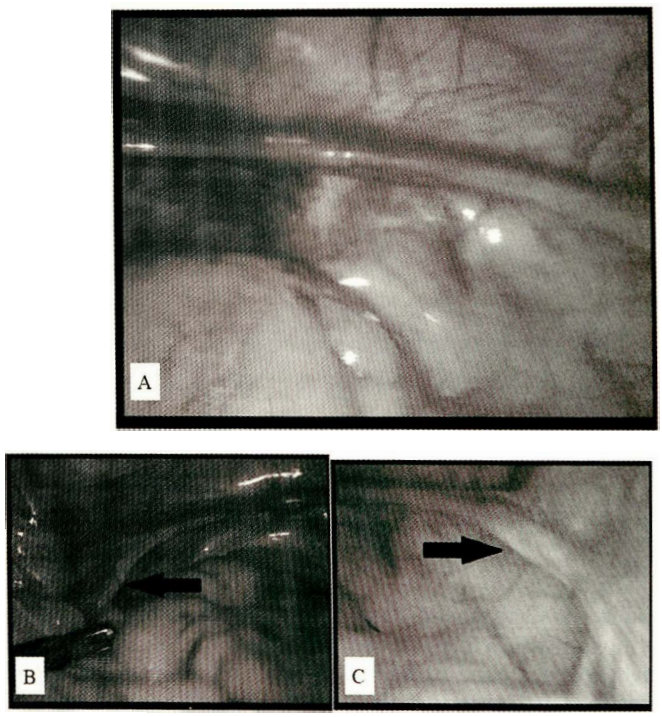

Figure 7. Laparoscopic findings of infantile uterus (A), left (B) and right (C) streak gonads.

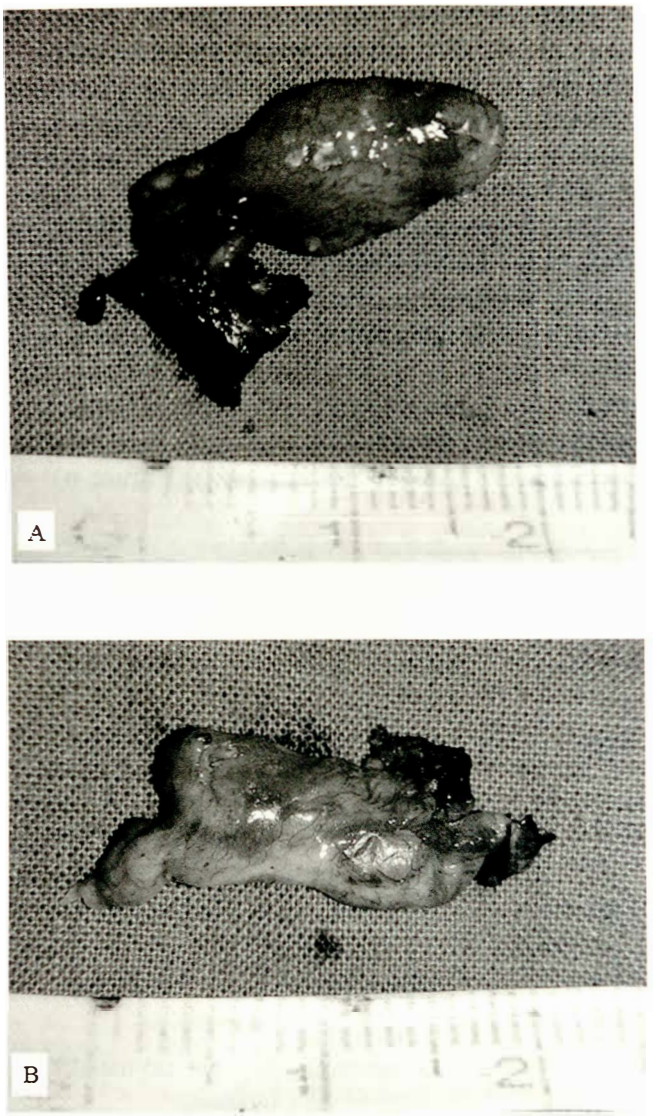

Figure 8. The right (A) and left (B) streak gonad each measured 2.0 cm x 1.0 cm x 1.0 cm.

Discussion

A. Disorder of Sexual Development

The disorders of sexual development (DSD), previously referred to as intersex disorders, are rare disorders with an incidence of 1:4,500 to 1:5,000 live births.[1] Many DSDs are associated with ambiguous genitalia, however, some may present with normal genitalia. The index patient consulted because of primary amenorrhea and delayed development of secondary sexual characteristics, but showed normal external female genitalia.

The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) consensus group proposed the classification of DSDs into: 1) Sex chromosome DSDs; 2) 46,XY DSDs (disorders of testicular development or disorders in androgen synthesis/action); and 3) 46,XX DSDs (disorders of ovarian development or fetal androgen excess).[16] The index patient belongs to the first type of DSD (i.e. 45X/46XY mixed gonadal dysgenesis).

B. Mixed Gonadal Dysgenesis (45XO/46XY mosaicism)

Mixed gonadal dysgenesis (45,X0/46,XY) is caused by chromosomal aberration known as mosaicism.[6] It is defined as the presence of two or more cell lines in the same individual. These cell lines are derived from a single stem line but with different chromosomal complements.[17] The clinical picture of mixed gonadal dysgenesis is heterogeneous, as the endocrine function of the testes can be affected to various degrees. The external genitalia can have a phenotype ranging from female to male.[6] In most cases, the gonads have developed asymmetrically, in which, a streak gonad can be seen on one side and normal or dysgenetic testes on the other side.[4] However, in some cases, the streak gonads are bilateral. It is assumed that the 45, XO cell line causes the development of the streak gonads and that the 46, XY cell line is associated with the differentiated testis.

It is assumed that mixed gonadal dysgenesis has an autosomal recessive inheritance pattern.[3] Autosomal recessive inheritance is used to describe a condition that appears only in individuals who have received two copies of an altered gene, one copy from the mother and another copy from the father. Their parents, each with a single copy of the altered gene, appear normal and are called heterozygotes or carriers of the altered gene.[18] The patient's pedigree chart (Figure 9) shows no evidence of phenotypic characteristics similar to the index patient. It remains undetermined if her parents or grandparents are carriers of the condition.

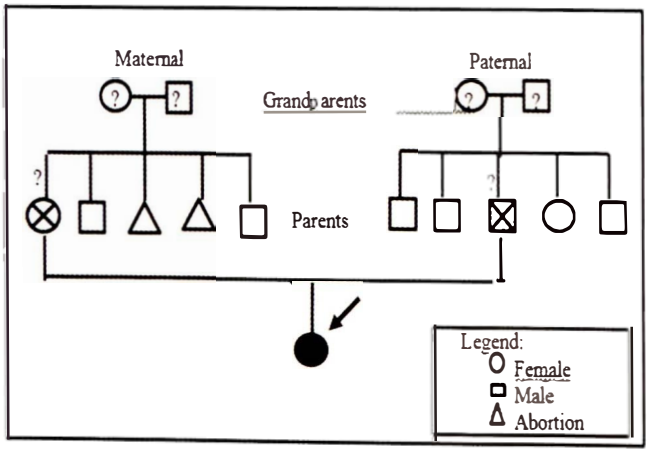

Figure 9. Patient M.P.'s pedigree chart.

From a genetic point of view, the most frequent form of mixed gonadal dysgenesis with chromosomal mosaicism (45,XO/46,XY) can be classified under Turner syndrome.[19,20] Therefore the typical features of the Turner syndrome such as the small stature and the absent secondary sex characteristics are found in these cases with mosaicism. The 45,XO component of the patient's chromosomal analysis explains the phenotypic features of the patient in this case including short stature, shield-like chest, wide-spaced nipples, cubitus valgus and delayed secondary sex characteristics (Tanner Stage 1 both for breast and pubic hair).

C. Pathophysiology

The genetic sex is determined by the chromosomal make up of an individual, which is either XX or XY. The Y chromosome contains the SRY (sex determining region), which induces male sex development during embryogenesis, especially the development of the gonads testes. In the absence of the SRY or in the presence of a second X chromosome, ovaries develop. This then determines the gonadal sex.[5,21,22] The te tes produce testosterone as well as the antimüllerian hormone (AMH), which suppresses the development of the mullerian ducts, precursors of the fallopian tubes, the uterus and the upper vagina. On the other hand, the ovaries produce estrogens. As a response to this hormone production of the testes or ovaries, the phenotypic sex develops.[21,22] Interestingly, recent studies showed that a number of genes have been identified that play a crucial role in sexual differentiation and that can lead to DSD or gonadal dysgenesis if mutated.

Development of either testes or ovaries depends on various genes that when slightest of mutation happens, disorders of sexual development and dysgenetic gonads may ensue. Specifically, mutation in the DHH of Desert Hedgehog Signal protein results into mixed gonadal dysgenesis. It is prudent to determine which gene is affected to confirm the suspected diagnosis of DSD. However, these tests are not readily available in the Philippines. Even if it were, the patient in this case may not be able to afford the high costs of these tests.

D. Diagnosis of Mixed Gonadal Dysgenesis

Thorough history and physical examination remain to be the cornerstone in diagnosing

patients with MGD. Clitoromegaly, size of the phallus, presence of hypospadias, and presence of palpable gonads should be noted as well as patency of vagina and evaluation of introitus. Genetic testing including chromosome analysis, FISH for SRY to evaluate cryptic Y mosaicism and genetic sequencing, hormonal evaluation (LH, FSH, AMH, testosterone) as well as imaging studies including pelvic ultrasound and magnetic resonance imaging (MRI) are of clinical value in assessing individuals with suspected syndrome. The index patient has normal-sized clitoris, no palpable inguinal or abdominal masses, 45XO/46XY karyotype, normal hormone assays and imaging and laparoscopic findings that showed infantile uterus and bilateral streak gonads, making mixed gonadal dysgenesis as the primary diagnosis.

E. Management Options of Patients with Mixed Gonadal Dysgenesis

Risk of Malignancy and Surgical Intervention

According to literature, 20%–30% of children with 46,XY complete gonadal dysgenesis (CGD) and 15%–20% of those with mixed gonadal dysgenesis (MGD) develop malignancies within the first twenty years of life. Therefore, streak or dysgenetic gonads are recommended to be surgically removed.[7,23] Furthermore, as stated by Ulrich, et al.[12], in all gonadal dysgeneses with Y-chromosomes, there is a certain risk for malignancy, which is why gonadectomy is indicated as early as possible.

Gonadoblastomas are the most common (25% rate of occurrence) tumors arising from intra-abdominal or intra-pelvic gonads.[24] These tumors are considered precursors to malignant seminomas and non-seminomatous germ cell tumors. In cases of a contralateral streak gonad or undescended gonad, there is an increased risk of bilateral tumor development. Therefore, a very important part of the treatment for these cases should be gonadectomy. In situations in which parents or patients do not wish to proceed with removal of the gonads, routine monitoring with ultrasound may be used to evaluate for development of malignancy. However, there are currently no established guidelines for monitoring patients who choose not to undergo gonadectomy. With regards timing of gonadectomy in patients reared as females, literature yields no unified approach on when is the best time to perform this procedure. Most studies recommend early gonadectomy in patients with (45XO, 46 XY) Turner syndrome. On the contrary, Cools, et al. in 2011 suggested that female patients with no signs of virilization have a low risk of developing a tumor (2.2%), so gonadectomy could be delayed in patients who are reluctant to undergo surgery.[13] This recommendation should be considered with caution as other studies have shown higher rates of malignancy in patients with (45XO, 46 XY) Turner syndrome.

Gonadal Biopsy

From 1985 to 2013, five observational studies were published tackling the role of gonadal biopsy in patients with gonadal dygenesis. Gonadal biopsy appears to be most useful in monitoring tumor development in mildly undervirilized males with testes. However, several limitations of gonadal biopsy must be taken into consideration. A study by Gourlay and colleagues noted that gonadal tumors can easily be overlooked on biopsy because of many different combinations of cells that may be found within the same individual gonad.

Limited sampling and sampling errors may also contribute to the limitations of gonadal biopsy especially in excluding the presence of small tumors.[26]

Given the irreversible nature of gonadectomy, ethical considerations must be taken into account. Risks, benefits and complications of the procedure should be discussed to the patient and family by a multidisciplinary team including specialists in endocrinology, gynecology, pediatrics, psychology and genetics. The patient was referred to the Psychiatry Department to assess her capability of understanding her medical condition and help her accept the implications of her diagnosis. Fortunately, the patient was assessed to have high intellectual and psychological capacity to understand and accept her condition. The patient had no signs of depression nor any major psychiatric problem. The patient was also referred to a Genetics counselor, who helped her understand the mode of inheritance of this condition.

Laparoscopy versus Laparotomy

According to recommendations gathered from several studies, laparoscopic approach of gonadectomy may be used and would be more beneficial to the patient. However, in cases where malignancy is suspected, i.e. in patients whose serum tumor markers including alpha fetoprotein (AFP), lactate dehydrogenase (LDH) and beta-human chorionic gonadotrophin (b-hCG) are elevated, staged surgical procedure in the form of laparotomy is indicated.[17] For the index patient, since malignancy was not considered, an operative laparoscopy with bilateral gonadectomy was done.

F. Hormone Replacement Therapy

There is limited information regarding the use of hormone replacement therapy in patients with mixed gonadal dysgenesis. However, several studies reported that in 90% of patients with Turner syndrome, hormone replacement therapy with estrogens and gestagens is used for the induction of secondary female sex characteristics and for the prophylaxis of chronic estrogen deficiency.[27,28,29] Furthermore, hypogonadism is common in patients with dysgenetic gonads as in the case of the index patient. Hormone replacement therapy is often required to induce development of secondary sexual characteristics and pubertal growth spurt, optimize bone mineral accumulation, and for psychosocial maturation in patients with DSD.[30] Estrogen can be given orally, by injection, or through patch. A progestin is usually added after breakthrough bleeding develops or within 1 to 2 years of continuous estrogen.

Estradiol valerate should be the first line therapy, followed by ethinyl estradiol.[12,20] In general, hormone replacement therapy should be continued until the natural onset of menopause as it promotes feminization and prevents osteoporosis.[27] Hormone replacement, in the form of estradiol valerate 2mg once a day, may be started post operatively to induce secondary sexual characteristics and pubertal growth spurt or even induce menstruation.

G. Psychosocial Support

Individuals who are genetically challenged need strong and constant support from their families. It is highly recommended that clinicians emphasize sensitive, supportive interactions with families, and full disclosure of the risks, benefits, and potential outcomes of intervention to allow them to participate as fully as possible in decision making and in the continuing care of the patient. Psychosocial care should be an integral part of management to promote positive adaptation. Other important resources include access to confidential sexual counseling and support groups. Regular follow-up from infancy or adolescence to adulthood regarding sexual, psychological, and social parameters is needed to provide a favorable long-term outcome for patients with DSD.

Summary and Conclusion

This is the case of an 18-year old college student, raised as a female, who presented with primary amenorrhea, delayed development of secondary sexual characteristics and classic features of Turner syndrome. Chromosomal analysis revealed a 45 XO/46 XY mosaicism, hence the diagnosis of mixed gonadal dysgenesis. Gonadectomy remains to be the definitive surgical management to prevent malignant degeneration of the dysgenetic gonads especially in mosaic individuals with Y-chromosome material. Furthermore, the gonads present in the patient in this case, are non-functional hence conservative monitoring may not be beneficial to the patient. Although there is controversy regarding the timing of gonadectomy, it is commonly recommended soon after diagnosis, with hormone replacement therapy started post-operatively. A multidisciplinary team composed of specialists in endocrinology, gynecology, pediatrics, psychology and genetics is very important in the management of patients DSD.

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