46, XY Partial Gonadal Dysgenesis Diagnosed In Adulthood

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Partial Gonadal Dysgenesis (PGD) is a rare disorder of sexual development defined by sexual ambiguity and the presence of mullerian structures due to variable degrees of testicular dysgenesis in individuals with a non-mosaic 46, XY karyotype. Due to incomplete gonadal development, the external phenotype would rely on the degree of testicular function. The dysgenetic gonads found in PGD have high risk for malignant transformation. Although ambiguous genitalia was noted upon birth, a case diagnosed in adulthood is presented. Discordance between sex of rearing and the psychosexuality of the patient prompted consult. On work up, 46, XY was noted on karyotyping but presence of a uterus was seen on ultrasound. Hormonal assay revealed elevated levels of FSH and LH, while testosterone levels were low and estradiol was high. Gonadoblastoma was noted on final histopathologic evaluation. This report shall tackle thorough preoperative evaluation, surgical and postoperative management of individuals with PGD.

Key words: Gonadal dysgenesis, disorders of sexual development, male pseudohermaphroditism

Introduction

Sexual differentiation is the process by which undifferentiated embryonic tissues develop into male and female sex organs. Normal sexual differentiation involves a sequence of related processes that begins with genetic or chromosomal sex, as established at the time of fertilization. Gonadal sex is determined next; directed by the chromosomal sex, the indifferent gonads differentiate into ovaries or testes. In turn, gonadal sex controls the hormonal environment of the embryo, which directs the development of the internal and external genitalia. These follow the male pathway in the presence of testicular hormones, or female pathway in their absence.[1,2] Factors disrupting any stage of these processes can lead to Disorders of Sexual Development (DSD).

DSD are congenital conditions of incomplete or disordered gonadal development leading to discordance between genetic sex, gonadal sex and phenotypic sex. It occurs with an estimated incidence of 1:5000.[3]

A unique subset of DSD is gonadal dysgenesis (GD), which is described as the incomplete or defective formation of gonads due to either structural or numerical anomalies of the sex chromosomes or mutations in the genes involved in gonadal development. The resulting dysgenetic gonads are characterized by variable degrees of immaturity and dysfunction and can thereby manifest in a wide range of genital ambiguity. Gonadal dysgenesis can be classified as either complete or partial depending on the morphology of the gonads.[4] Complete gonadal dysgenesis, or Swyer syndrome, is the absolute failure of the gonads to develop resulting in a female phenotype in an individual who is genetically male.

Partial Gonadal Dysgenesis (PGD) is a rare disorder characterized by sexual ambiguity usually

with mullerian structures due to variable degrees of testicular dysgenesis in individuals with a non-mosaic 46, XY karyotype. The external phenotype would depend on the degree of gonadal function.[4,5,6,7]

Patients with PGD have a 25% risk for developing germ cell tumors due to the presence of dysgenetic gonads with the Y chromosome.[8] Gonadoblastoma is the most common tumor seen in patients with XY GD. This neoplasm was first described by Scully in 1953 and was said to resemble a developing gonad. Though benign, 50-60% of gonadoblastoma have the propensity for malignant transformation.[4,9,10] To prevent the development of malignancy in patients with PGD, the recommendation would be to perform gonadectomy; however, current debate ensues with regards to patient selection and timing of intervention.

Presented is a case of DSD diagnosed in early adulthood, presenting with ambiguous genitalia and a small uterus. The clinical, cytogenetic, endocrine, and histopathologic data gathered are consistent with partial gonadal dysgenesis. Bilateral gonadoblastoma was noted on further histopathologic evaluation.

The Case

The patient is BD, a 22-year-old Filipino male from Pangasinan who consulted for ambiguous genitalia. He has no known hypertension, renal disease, cardiac disease, or blood dyscrasias. He has an unremarkable past medical and family history. BD is the third of four siblings, delivered by a traditional birth attendant to a then 30-year-old mother with no known illnesses. There was no exposure to maternal virilization or to androgenic drugs in utero. An ambiguous genitalia was already noted at the time of birth, as noted by presence of both penis and a vagina; however, his parents decided to rear him as a female.

By age 12 years, BD began exhibiting male behavior: he was attracted to females, showing preference to male sports activities and cars. He stopped wearing skirts and preferred pants instead to hide his phallus, which had begun to increase in size and erect. BD noted his voice began to deepen. He was then brought to the pediatric clinic, consulting initially for absence of breasts and amenorrhea. Karyotyping done revealed 46, XY and hormonal work up revealed elevated FSH and LH and normal testosterone. The impression then was Disorder of Sexual Development but the patient was lost to follow up before any further work up was done.

Since he was about to finish college, he wanted to commit into a relationship with a woman and planned to enter the Philippine National Police (PNP), BD sought consult once again and was referred to the gynecologic clinic for management. BD weighed 50 kilograms with a height of 168cm (Figure 1). There was note of severe acne on the face and presence of laryngeal prominence. Systemic physical examination findings were essentially normal. Secondary sexual characteristics noted were dense axillary hairs, dense pubic hair in a triangle shaped pattern Tanner 5, moustache comprised of thin scanty hair. Absence of breasts was noted, Tanner 0 (Figure 2). On examination of the external genitalia, there was a prominent curved phallus with a 5cm glans penis with redundant preputial skin. The urethral meatus was located at the base of the glans. There were prominent labia majora and hypoplastic labia minora (Figure 3). A 2-cm rudimentary vagina was noted with no palpable cervix. There were no palpable masses at the labia and inguinal area.

A transrectal sonologic examination revealed a 2.8 cm - long vagina. There was note of a small uterus with cervix and thin endometrium (Figure 4). The gonads were small and seemingly streaked (Figure 5). Compact hypoechoic masses were noted at the base of the penile shaft lateral to the urethra measuring 1.1cm x 1.2 cm x 0.6cm and 1.3cm x 1.4cm x 0.9cm. The sonologic impression was: Normal uterus with thin endometrium; streaked ovaries; bilateral masses probably testes. To further investigate the labial masses, an MRI was done showing paired midline tubular structures probably representing the corpora cavernosa of an enlarged clitoris (Figure 6).

Hormonal assay revealed that Serum FSH and LH were elevated at 25.7 uIU/ml (normal range 1.0-10.5 uIU/ml for male) and 24.6 uIU/ml

(normal range 1.9-9.4 uIU/ml, male), respectively; while serum testosterone was normal at 17.1 nmol/L (normal range 9-38 nmol/L) but falls below the 10th percentile for normal testosterone levels for males less than 25 years of age. Serum estradiol was elevated at 85 pg/ml (normal range for male: 0 pg/ml). DHEA, DHT were normal. AMH was elevated at 7.566 (normal range 0.3-4.0 ng/ml).

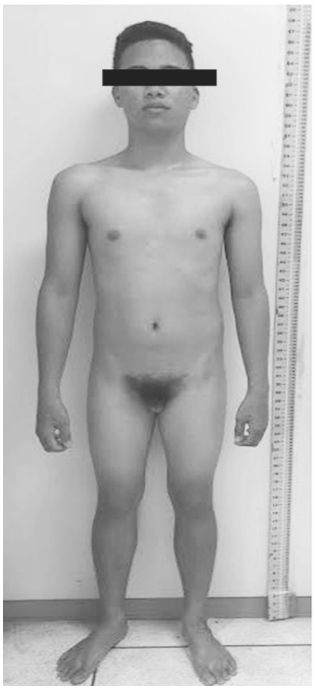

Figure 1. Whole body picture of the index patient. The patient is phenotypically male except for the female pattern distribution of pubic hair. He has lean body mass and normal stature of an adult male (168cm).

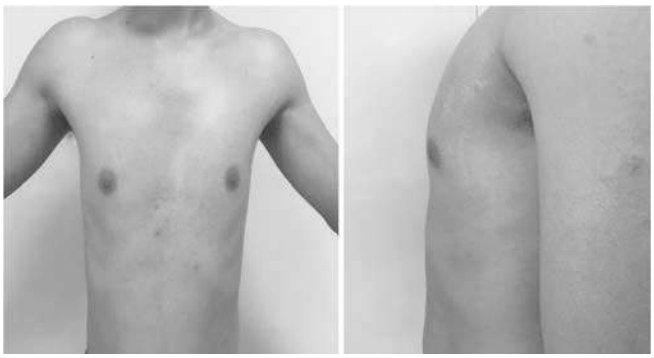

Figure 2. Breast development of index patient. There are no breast buds.

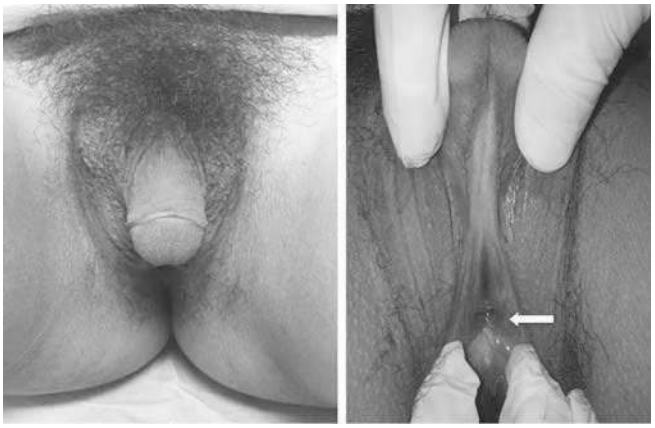

Figure 3. External Genitalia of the index patient. There was a prominent curved phallus with redundant preputial skin and perineoscrotal hypospadias. Labia majora, hypoplastic labia minora, introitus (arrow) to a 2-cm rudimentary vagina were noted.

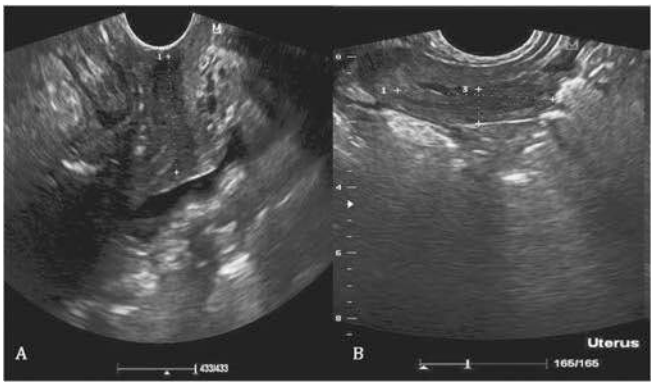

Figure 4. Tranrectal ultrasound of the vagina measuring 2.8cm (A) and uterus with small cervix and thin endometrium (0.1cm) measuring 4.9cm x 2.4cm x 1.1cm (B).

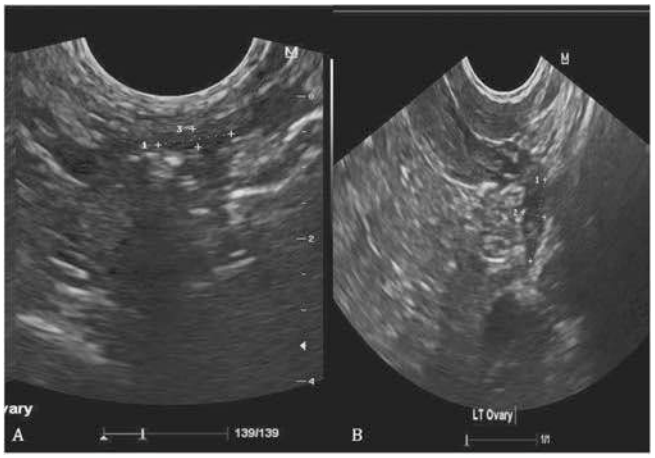

Figure 5. Tranrectal ultrasound of the right gonad (A) measuring 0.9cm x 0.8cm x 0.3cm and left gonad (B) measuring 1.1cm x 0.7cm x 0.6cm.

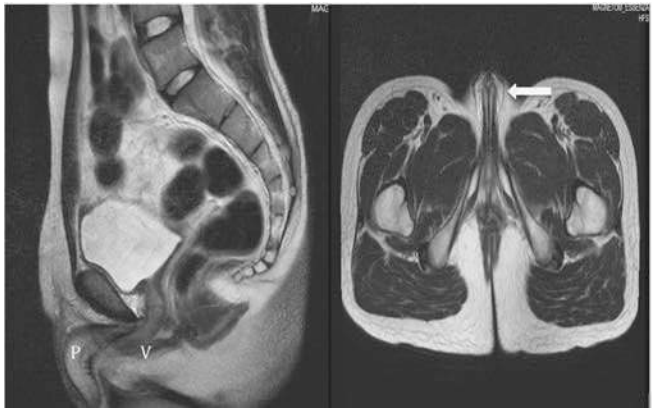

Figure 6. Pelvic MRI in sagittal and transverse view. Note the vagina (V) and the phallus (P) on sagittal view. Transverse view showed corpora cavernosa (arrow) which was initially thought to be labial masses.

Primary working impression at this time was 46, XY Ovotesticular DSD based on the presence of testosterone and high estradiol levels. Differential diagnosis was 46, XY partial gonadal dysgenesis because of the hypergonadotropism despite supposedly normal levels of testosterone indicating that there is possibly insufficient testosterone production hence the lack of negative feedback to the pituitary.

The patient was then referred to IM Endocrinology, Urology and Genetics. A multidisciplinary conference was held. Tumor markers were requested and revealed slightly elevated LDH. An HCG challenge test was done which yielded minimal rise in testosterone levels, favoring the impression of 46, XY PGD. The plan for the patient was for total laparoscopic hysterectomy with bilateral gonadectomy, and repair of hypospadias.

The patient underwent subtotal laparoscopic hysterectomy, bilateral gonadectomy, and first stage repair of hypospadias. Intraoperatively, the right gonad was smooth with a mixture of white and grey colored tissue measuring 2.5cm x 1.8cm x 1cm (Figure 7). The left gonad was a white smooth tissue measuring 1.5cm x 1cm x 1cm (Figure 8). The uterus was small, measuring 2.5cm x 4cm x 1 cm, with smooth serosal surface (Figure 9). Cut section of the uterus revealed smooth endometrium measuring 0.1 centimeter. The myometrium measured 1 cm anteriorly and posteriorly. The uterine cavity was 2 centimeters deep. Both fallopian tubes appeared normal. The rest of the abdominal organs appeared grossly normal.

Microscopic evaluation confirmed mullerian structures: fallopian tubes (Figure 10) and uterus with inactive endometrium (Figure 11). Final histopathologic evaluation of the gonads with immunohistochemical staining revealed bilateral gonadoblastoma.

The postoperative course was unremarkable. BD was discharged after 2 days and has been receiving intramuscular testosterone during follow up visits at 2-week intervals.

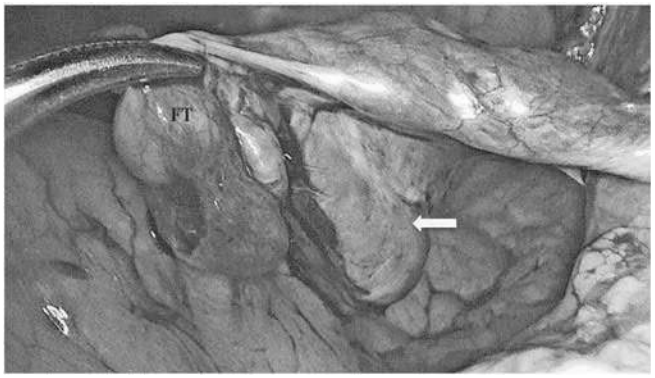

Figure 7. Right gonad on laparoscopy. The right gonad (arrow) is seen in proximity to the distal end of the fallopian tube (FT).

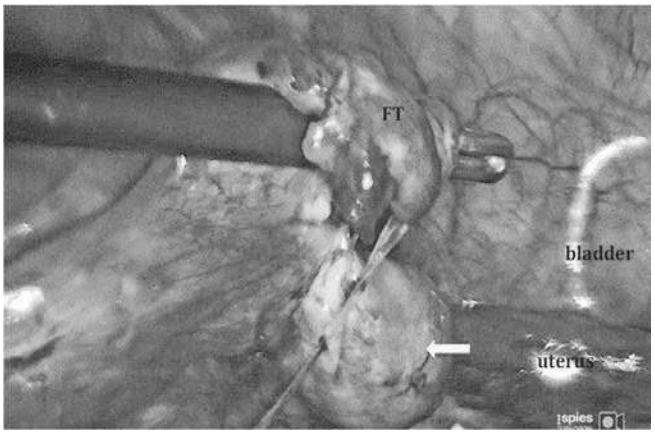

Figure 8. Left gonad on laparoscopy. The left gonad (arrow) is seen in proximity to the distal end of the fallopian tube (FT). There were adhesions on the fimbriated end of the tube.

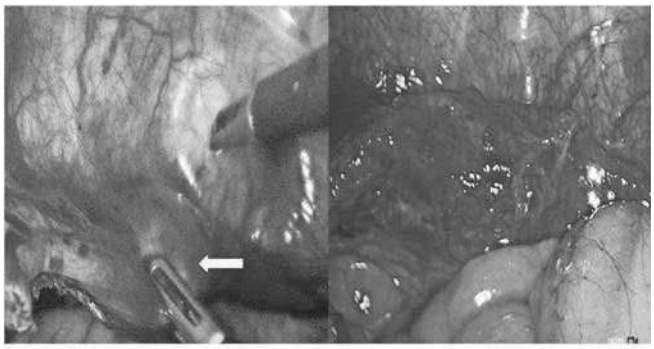

Figure 9. Uterus on laparoscopic view. The uterus is small in size. It was anteflexed. The fundal end was grasped by blunt forceps (left) for a better view.

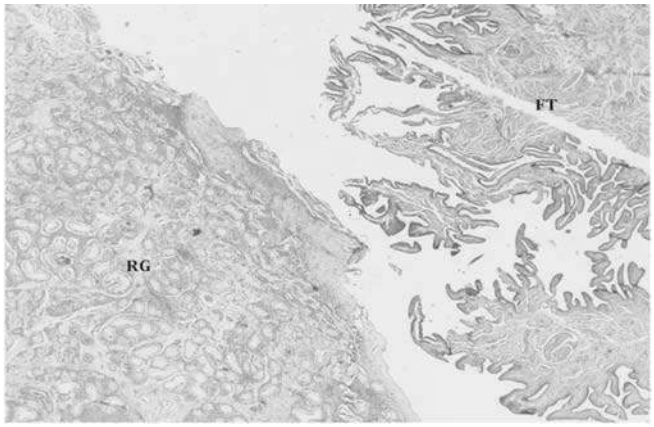

Figure 10. Microscopic view of the right dysgenetic gonad (RG) and fallopian tube (FT). RG consists of numerous seminiferous tubules containing scant spermatogonia and prominent Sertoli cells. (*Haematoxylin eosin stain*, 20x)

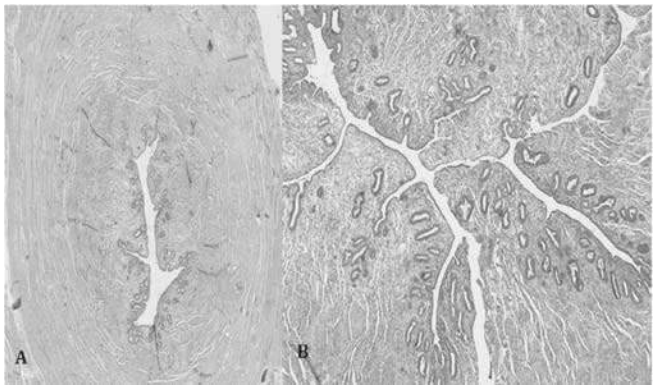

Figure 11. Microscopic view of the uterus. A. Cut sections of the uterus reveals eosinophilic fibromuscular walls encircling the endometrium (myometrium). B. Endometrium consisting of tubular endometrial glands exhibiting no mitotic activity in a moderately cellular stroma. (Haematoxylin eosin stain, A-20x, B-40x)

Discussion

Partial Gonadal Dysgenesis (PGD) is defined by incomplete testis determination in an individual with a normal male karyotype. This condition has been referred in the past as *dysgenetic male pseudohermaphroditism* or 46, XY mixed gonadal dysgenesis. It is important to distinguish this condition from 45, X /46, XY mixed gonadal dysgenesis in which the pathology is related to mosaicism.[2,7] The prevalence for PGD is unknown. Locally, there are no reports of PGD in literature although Hamin, et al. reported a similar case of 46, XY DSD presenting with ambiguous genitalia, dysgenetic gonads but without mullerian structures.[8]

The clinical presentation of PGD includes ambiguous genitalia with a wide spectrum of masculinization due to the variable degrees of testicular dysgenesis. This may range from a seemingly female phenotype with clitoromegaly to a male phenotype with isolated hypospadias. Syndromic picture is absent in these cases.[2,4,5,6,7] An utriculo-vaginal pouch is present in a large number of patients. Proliferation of Wollfian structures would depend on the extent of testosterone secretion of the embryo, whereas the extent of Mullerian duct development depends on the secretion of AMH.[7]

Genetic testing should be done in suspected cases of PGD. Analysis of a sufficient number of cells during karyotyping is imperative to rule out mosaicism with a high degree of confidence.

The hormonal picture of PGD is hypergonadotropic hypogonadism with significantly high LH and FSH levels at the age when puberty naturally occurs. It is typical for individuals with PGD to have a diphasic pattern of LH and FSH secretion whereby gonadotropins are elevated during infancy, fall to nearly normal values in childhood and return to high levels after puberty. Measurements of serum testosterone and Anti-Mullerian Hormone (AMH) are usually decreased and the hCG stimulation test induces minimal to no elevation in testosterone as response.[4]

In addition to karyotyping and hormonal assays, McCann-Crosby, et al. recommend imaging to aid in the diagnosis of PGD. Pelvic ultrasound or Magnetic Resonance Imaging (MRI) will aid the clinician in to evaluating internal genital anatomy and gonadal position as part of preoperative planning.[4]

Gonads are most often intraabdominal although some may be found in the inguinal area or in the scrotum. The histology may vary from gonads with a few, disordered, tubular structures, incomplete formation of the tunica albuginea and predominance of fibrous tissue to those with mild abnormalities. The dysgenetic gonads may be found bilaterally or associated with streak gonads.[2,4,6,7,9]

The exact etiology of PGD is still unknown. Mutations in the SRY (Sex determining region Y) gene are rarely seen in PGD unlike in many cases of CGD. In recent studies, both heterozygous and homozygous mutations in NR5A1 (Nuclear Receptor Subfamily 5, Group A, Member 1) gene, which codes for the SF1 (Steroidogenic factor 1) protein responsible for testicular differentiation, have been found in only 15% of patients with PGD.[2,5]

Differential diagnoses for PGD include mixed gonadal dysgenesis (MGD) and Ovotesticular DSD (OT-DSD). PGD and MGD share similar gonadal and genital features; however, in MGD there is mosaicism with a 45, X cell line and one or more lineages with a normal or structurally abnormal Y chromosome.[2,5,7] Consequentially, patients with MGD may typically show features of Turner's syndrome; namely, short stature, dymorphisms, cardiovascular and renal malformations.[5] OT-DSD and PGD share the same clinical presentation: ambiguous genitalia and a mix of wolffian and mullerian duct structures depending on the extent of testicular development. The diagnosis of OT-DSD can only be confirmed by the presence of gonads that contain well-developed ovarian and testicular tissues on histopathologic evaluation. hCG stimulation test can be used to differentiate OT-DSD from other DSDs, since developed ovarian and testicular tissues are present, a normal response is expected from these cases.[12]

The index patient, BD, presented with ambiguous genitalia with a well-developed phallus, 2cm vagina and pernineoscrotal hypospadias. He was generally phenotypically male but with a uterus small for age. Pelvic imaging noted bilateral gonads, initially assessed as streak ovaries. Karyotyping revealed 46, XY with no mosaicism. Hormonal assay showed hypergonadotropism with testosterone levels that fluctuate from low to normal and elevated estradiol levels for male. Adrenal steroid biosynthesis defects were ruled out. The impression was initially 46, XY OT-DSD due to the elevated levels of serum estradiol that could imply presence of ovarian tissue. However the significantly elevated FSH and LH pointed to a more possible diagnosis of PGD. An hCG stimulation test resulted in a minimal rise in testosterone favoring the diagnosis of PGD. A team of experts was formed consisting of reproductive medicine, urology, endocrinology, and psychiatry. To address the many concerns in the management of PGD, or DSD in general, a multidisciplinary approach is crucial.

The first issue raised was the gender identity of the patient. Sexual ambiguity is noted upon birth of an infant. Although ethicists and patient support groups advocate that genital surgery should be delayed to a time when the individual is able to comprehend and make an informed decision instead of immediate repair in infancy, a bisexual phenotype causes a lot of stress for both patient and his family.[11] Evaluation should be initiated early into childhood. Failure to address gender identity can lead to psychosexual dilemma, emotional distress and the risk of social isolation, embarrassment and discrimination in the adult years.[8] BD has already experienced the emotional torment during his adolescent life, torn by the guilt of being attracted to the opposite sex and confused by the presence of a growing phallus. It is fortunate that BD has developed a strong sense of gender identity despite late evaluation of his DSD. The condition that distressed him the most during his early adult life was having to urinate sitting down and the awareness of the presence of a vagina. Long-term psychosocial support is an important part of the management of DSD in order to openly

address dissatisfaction with body image, ensure quality of life and other concerns.

The next issue addressed is the surgical plan. Management of PGD cases definitely includes surgical correction of the external genitalia, depending on the patient's chosen gender identity. There is also a need to remove mullerian structures as they can give rise to malignancy in 3 to 8% of cases[12]; in addition to the psychological impact of having internal structures of the opposite sex. It has been argued that dysgenetic gonads could be brought into the scrotum via orchiopexy depending on the location of the gonads. Although the risk for malignancy remains, the development of the tumors can be ascertained more easily by physical examination of the scrotum during regular follow up and serial scrotal ultrasound scans.[7] The dysgenetic testes may produce testosterone to an extent but testosterone therapy is still often necessary. For BD, the initial plan was to attempt orchidopexy; yet due to the unfavorably high position of the gonads and the possibility of malignancy in dysgenetic gonads, total laparoscopic hysterectomy with bilateral gonadectomy and primary repair of hypospadias was decided. Laparoscopy is widely used for the exploration of gonads as it provides good exposure and access to pelvic structures thereby facilitating straightforward identification and complete removal of potentially malignant gonads and mullerian remnants with minimal blood loss and shorter hospital stay. For the patient, the aesthetics of having small incisions meant the most to him since he wanted to join the PNP and he hoped traces of his surgery would go unnoticed.

On thorough histopathologic evaluation, bilateral gonadoblastoma were noted. Gonadoblastoma is the most common germ cell tumor seen in patients with XY gonadal dysgenesis. The risk of gonadal tumors in PGD is 16-30%.10 Gonadoblastoma usually presents in the second decade but can also present in infancy though rare.[7,10] Microscopically, it presents with a mixture of germ cells and stromal elements as well as

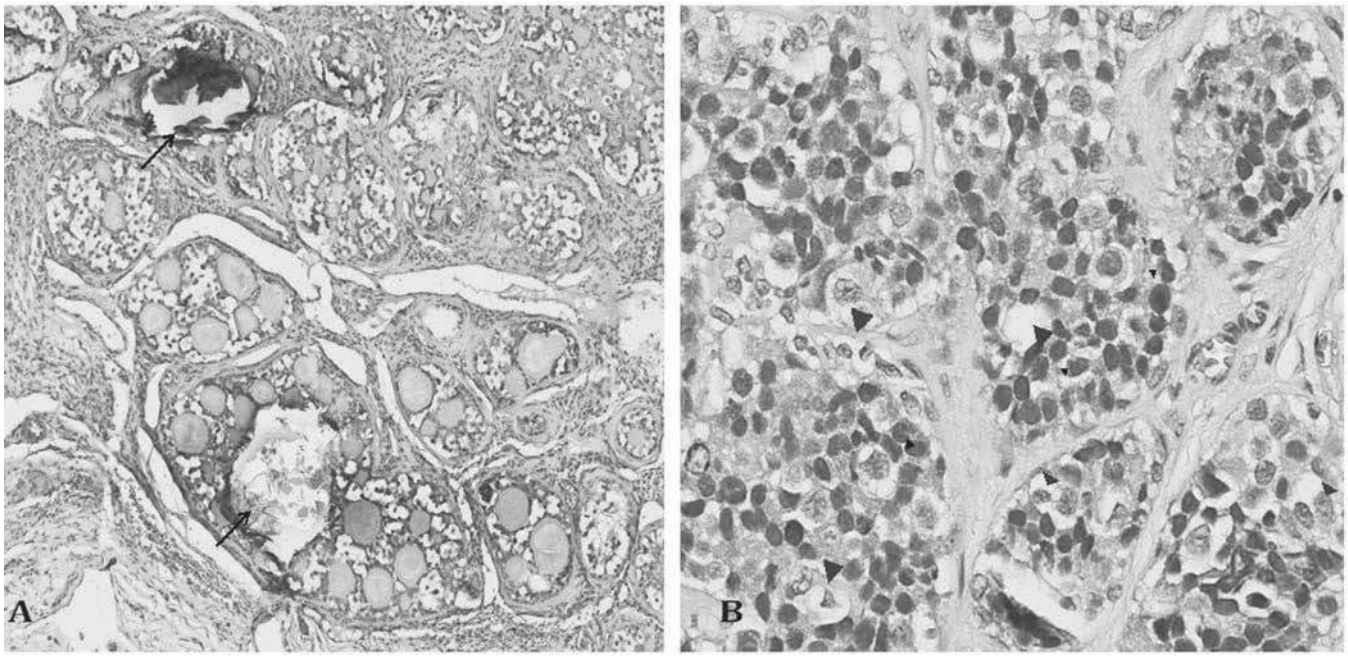

Figure 12. Microscopic view of the dysgenetic gonads. A. The right gonad consists of groups of well-defined nests in a fibrous stroma composed of two populations of cells, with well-defined eosinphilic hyaline basement membrane-like material similar to the left gonad. Foci of calcifications are seen (black arrow). B. The left gonad consists of well defined nests that are composed of a heterogeneous population of cells: primitive germ cells (black arrow heads) and primitive sex-cord stromal derived cells (black arrowheads). (Haematoxylin eosin stain, A - 200x; B - 400x)

immature Sertoli cells and may contain calcifications as seen in the index patient (Figure 12). Invasion of stroma leads to the diagnosis of dysgerminoma or seminoma occurring in 50% of cases. 4, 10, 11 Fortunately in the case of BD, the gonadoblastoma was not associated with malignant germ cell tumors. If the gonadoblastoma were detected preoperatively, then gonadectomy would have been the surgical plan from the outset due to the high association with malignancy.

The possibility that the gonadoblastoma may secrete estrogens has been noted but only on the basis of the occurrence of hot flushes and other menopausal symptoms after excision of the tumor. It has also been shown that gonadoblastoma, ascribed to the Leydig or lutein-like cells, is capable of producing testosterones and estrogens from progesterone in vitro.[10] This could possibly explain the elevated estradiol levels of the index case in retrospect. Prognosis of patients with pure gonadoblastoma is excellent, provided the tumor and the contralateral gonad, which may be harboring an undetected gonadoblastoma, are excised. The risk of bilateral occurrence is estimated at 40% or higher.[10]

BD was discharged improved and received testosterone injections on follow up. Hormonal replacement therapy is necessary after gonadectomy in order to maintain sex-specific secondary sexual characteristics, have optimal bone mineral mass accumulation, induce sex-specific psychosocial and psychosexual maturation, which could lead to a normal social and sexual life.[13]

Conclusion

Partial gonadal dysgenesis a very rare condition that is defined by the incomplete differentiation of the testis in individuals with non-mosaic 46, XY karyotype. It presents with ambiguous genitalia with or without persistent mullerian structures. PGD is associated with high levels of FSH and LH with low to normal testosterone. Dysgenetic gonads in PGD are at increased risk for developing germ cell tumors, the most common of which is gonadoblastoma. Gonadoblastoma has increased potential for malignant transformation in 50% of cases.

Management of PGD, or DSD in general, includes establishing gender identity, correction of the external genitalia based on the chosen gender, minimizing risks for malignancy, preserving fertility when possible and conserving the ability to have satisfactory sexual relationships.

The index patient was born with ambiguous genitalia but evaluation was delayed until adulthood. Persistent mullerian structures were noted on imaging. A multidisciplinary team composed of gynecologists, urologists, endocrinologists and psychiatrists was created to come up with an appropriate management for this case. Surgery was performed to eradicate risk for malignant transformation of his dysgenetic gonads and histopathologic data confirmed the diagnosis of PGD with additional findings of bilateral gonadoblastoma. The complete excision of both gonads ensures good prognosis. BD receives testosterone therapy every 2 weeks, and is currently preparing for the second stage repair of his hypospadias.

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