46, XY PARTIAL GONADAL DYSGENESIS DIAGNOSED IN ADULTHOOD

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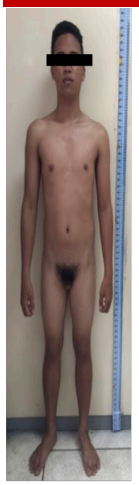
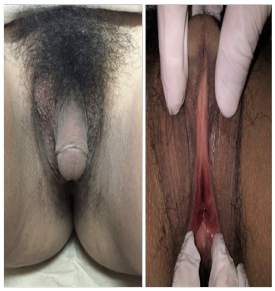
ABSTRACT

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 nonmosaic 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 a high risk for malignant transformation, especially when located intraabdominally. Although ambiguous genitalia are noted upon birth, we present a case that was diagnosed in adulthood. The patient was reared as a female but experienced growth of phallus at the onset of puberty. Discordance between sex of rearing and the psychosexuality of the patient prompted consult during adulthood. 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.

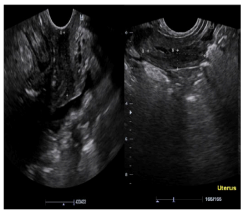
CASE PRESENTATION



A 22-year-old, 46, XY presented at the gynecologic clinic with ambiguous genitalia. There was note of severe acne on the face and presence of laryngeal prominence. Secondary sexual characteristics noted were dense axillary hairs, dense pubic hair in a triangle shaped pattern (Tanner 5), thin scanty hair upper lip hair. Absence of breasts was noted (Tanner 1). FSH , LH , Estradiol were elevated. AMH, Testosterone, DHEAS, DHT were normal.

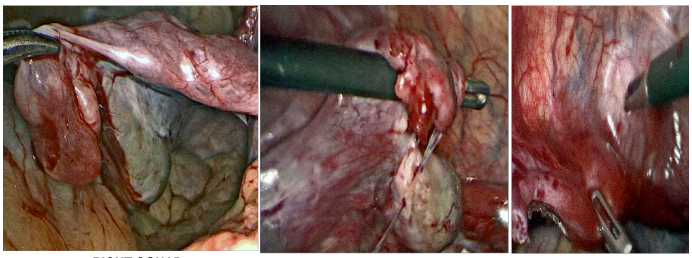


External Genitalia of the index patient. There was a prominent curved phallus with redundant preputial skin and perineoscrotal hypospadias. Labia majora, hypoplastic labia minora, introitus (arrow) to a 2-cm rudimentary vagina were noted.

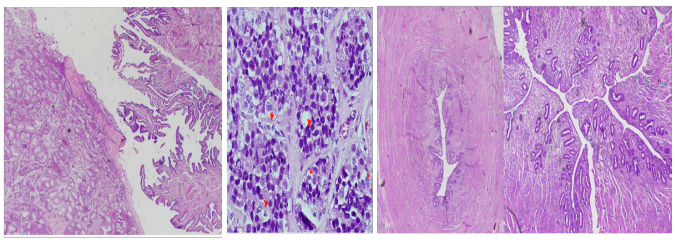


Tranrectal ultrasound of the vagina measuring 2.8cm and uterus with small cervix and thin endometrium (0.1cm) measuring 4.9 x 2.4 x 1.1cm. The right gonad measured 0.9 x 0.8 x 0.3 cm and left gonad measured 1.1 x 0.7 x 0.6 cm.

Primary working impression was initially 46, XY Ovotesticular DSD due to the elevated levels of serum estradiol that could imply presence of ovarian tissue. However the persistently elevated FSH and LH pointed to a more probable diagnosis of PGD. 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 2.5 x 1.8 x 1 cm. The left gonad contained white smooth tissue measuring 1.5 x 1 x 1 cm. The uterus was small, measuring 2.5 x 4 x 1 centimeters, with smooth serosal surface. Cut section of the uterus revealed smooth endometrium measuring 0.1 centimeter.



RIGHT GONAD | LEFT GONAD | UTERUS



Microscopic evaluation of the right gonad (A) revealed numerous immature seminiferous tubules containing scant spermatogonia and prominent Sertoli cells. The left gonad (B) consists of well defined nests that are composed of a heterogeneous population of cells: primitive germ cells (red arrowheads) and primitive sex-cord stromal derived cells. Fallopian tubes were noted (A, black arrow) and with inactive endometrium (C) were seen. Final histopathologic evaluation of the gonads with immunohistochemical staining revealed bilateral gonadoblastoma.

Diagnosis of PGD was confirmed based on histopathology results of immature testes and bilateral gonadoblastoma. Ovotesticular DSD was ruled out due to the absence of ovarian tissue. Gonadoblastoma can be hormonally active and secrete estrogens and androgens, which may mask gonadal dysgenesis and delay diagnosis such as in this case. The patient was discharged improved and given testosterone biweekly.

CASE DISCUSSION

Clinical presentation of PGD includes ambiguous genitalia with a wide spectrum of masculinization due to the variable degrees of testicular dysgenesis. 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. 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.

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.

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. Consequentially, patients with MGD may typically show features of Turner's syndrome. OT-DSD and PGD share the same clinical presentation but diagnosis of OT-DSD can only be confirmed by the presence of both ovarian and testicular tissue on histopathologic evaluation.

The index patient, BD, presented with ambiguous genitalia with a well-developed phallus, 2cm vagina and pernineoscrotal hypospadias. He was 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.

Surgical correction of the external genitalia depends on the patient's chosen gender identity. Removal of mullerian structures is warranted as they can give rise to malignancy in 3 to 8% of cases. 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. The dysgenetic testes may produce insufficient testosterone; hence, 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 done.

On 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%. Gonadoblastoma usually presents in the second decade but can also present in infancy though rare. Microscopically, it presents with a mixture of germ cells and stromal elements as well as immature Sertoli cells and may contain calcifications as seen in the index patient. Invasion of stroma leads to the diagnosis of dysgerminoma or seminoma occurring in 50% of cases. Gonadoblastoma, ascribed to the Leydig or lutein-like cells, is capable of producing testosterones and estrogens from progesterone in vitro. 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.

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.

CONCLUSION

Partial gonadal dysgenesis a very rare condition that is defined by the incomplete differentiation of the testis in individuals with nonmosaic 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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