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Case Report
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A Rare Case of Partial Gonadal Dysgenesis (46,XY) from Pakistan

ABSTRACT:

46XY Partial gonadal dysgenesis(PGD) is a rare subset of disorders of sexual development (DSD). Diagnosing and managing such cases can be particularly challenging in resource-limited settings like Pakistan. We present the case of a 17-year-old male with ambiguous genitalia and hypospadias. On presentation, he was diagnosed with perineal hypospadias, rudimentary blind ending vagina, asymmetric testicular descent and a hypoplastic prostate. Hormonal tests revealed high levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and low testosterone, and imaging studies showed a normal bladder shape but no prostate. Surgical treatment was performed in two steps. Stage one consisted of scrotoplasty, urethroplasty, chordea correction, and grafting. The second operation involved tubular reconstruction of the urethra. Along with that, we also gave hormone replacement therapy for testosterone deficiency and sent the patient for psychological counselling. To our knowledge, no previously published cases of PGD have been reported from Pakistan. Nevertheless, a complete gonadal dysgenesis (Swyer Syndrome) case was described by Jawed et al in 2023. This case report describes this patient's unique presentation, thereby exemplifying the wide spectrum of clinical findings and management difficulties of this case while adding to the scant literature on DSD in Pakistan, in hopes of providing insight to improve patient outcomes.

KEYWORDS: 46,XY Partial Gonadal Dysgenesis; Disorders of Sexual Development (DSD); Ambiguous Genitalia; Hypospadias; Hormonal Evaluation

INTRODUCTION:

Disorders of sexual development (DSD) are genetic disorders characterized by errors in the development of chromosomes, gonads and phenotypic sex.[1] 46,XY DSD is associated with defects in androgen synthesis, metabolism, or receptor function, resulting in ambiguous genitalia in genetic males.

The incidence of DSD is estimated to be 1 in 4,500-5,500 births globally[2] but is underrepresented in Pakistan due to social stigma and limited diagnostic resources. We report a rare case of 17-year-old male with ambiguous genitalia that emphasizes the challenges of diagnosis, surgical management and psychosocial issues related to this case, thereby contributing to the established literature.

CASE PRESENTATION:

A 17-year-old boy presented to the Outpatient Department in Lyari General Hospital (a tertiary care hospital in Karachi) with complaints of scrotal hypospadias and erectile dysfunction (ED) with no discharge. The patient had a 46, XY karyotype and presented with underdeveloped male secondary sexual characteristics. Family and psychosocial history were unremarkable.

Physical examination revealed small sized penis and glans and bifid scrotum. The urethral opening was present on the undersurface of penis. The right testis was partially descended, and the left testis was palpable in the left inguinal pouch. On ultrasound prostate was absent, and the shape and size of the bladder were normal. Karyotyping was performed, which showed a 46, XY. Hormonal profile revealed high FSH (19.12 IU/L) and LH (8.24 IU/L) levels with low serum testosterone [Table 1]. Cystoscopy revealed a rudimentary blind ending vagina, no prostate and normal bladder capacity and neck. All routine lab investigations (CBC, EKG, LFT, HBsAg, Anti-HCV, UCE, and CXR) were normal.

TABLE 1. Serum, Thyroid, and Fertility Profile Results

Investigation	Category	Reference Value	Patient Value
TLC (cells/mm³)	Serum	4–11	6.7
Hemoglobin (g/dL)	Serum	11.5–17.5	12.1
Sodium (mmol/L)	Serum	135–150	140
Potassium (mmol/L)	Serum	3.5–5.1	4
Total bilirubin (mg/dL)	Serum	0.1–1.0	0.6
ALP (U/L)	Serum	35–104	195
ALT (U/L)	Serum	10–150	34
Blood urea (mg/dL)	Serum	10–50	35
Creatinine (mg/dL)	Serum	0.42–1.06	0.8
FSH (IU/L)	Fertility	1–10	19.12
LH (IU/L)	Fertility	1.6–8.3	8.24
Prolactin (IU/L)	Fertility	2–26	16
Testosterone (IU/L)	Fertility	0.4–0.45	0.38 (borderline low)

Abbreviations: WBC = White blood cells; ALT = Alanine transaminase; ALP = Alkaline phosphatase; FSH = Follicle-stimulating hormone; LH = Luteinizing hormone.

The patient was then referred to the Urology department and admitted for surgical intervention. A two-stage surgical repair was performed. In stage 1 procedure, scrotoplasty and 1st part of urethroplasty were performed in which perineal hypospadias was corrected. The procedure was successful, and the patient was scheduled for the second stage of surgery, which would involve forming a functional urethral tube and correcting additional genital abnormalities. Follow-up was recommended to ensure ongoing treatment and follow-up.

Figure 1: Rudimentary Blind-ending vagina

DISCUSSION:

A literature search through PubMed yielded no results for this case in Pakistan before. However, a case of Swyer syndrome was reported in 2023 by Jawed et al.[3]

46XY Disorders of sexual development (DSD) is a broad clinical term for conditions that are associated with abnormal development of chromosomes, gonads, and phenotypic sex.[3] Partial gonadal dysgenesis PGD is uncommon, a subset of gender development disorder with atypical presentation in the development of gonads resulting in ambiguous genitalia from a fully female phenotype with 46XY karyotype or partial male or fully male phenotype with 46XY karyotype.[4]

The gene SRY on the Y chromosome is a key actor in male sex determination, starting from testis development. 10–20% of cases have a missense mutation in the SRY gene (which, if functional, will lead to opposite gender genitals or externally female characteristics), leading to complete gonadal dysgenesis and ambiguous genitalia. Moreover, additional genes, including SOX9 and NR5A1 and many others, are also sporadically mutated, which increases the likelihood of phenotypic variations in this condition, 46XY DSD.[5] PGD is often idiopathic; however, NR5A1(Nuclear Receptor Subfamily 5, group A member 1) mutations are supposed to be mostly involved. According to recent studies, these are reported in 15% of PGD patients. NR5A1 encodes SF1(steroidogenic factor which is responsible for testicular differentiation.[6]

The SOX9 gene is thought to be the second most important component, next to SRY in male sexual differentiation, such that mutations often lead to ambiguity or female external genitalia in 46XY subjects.

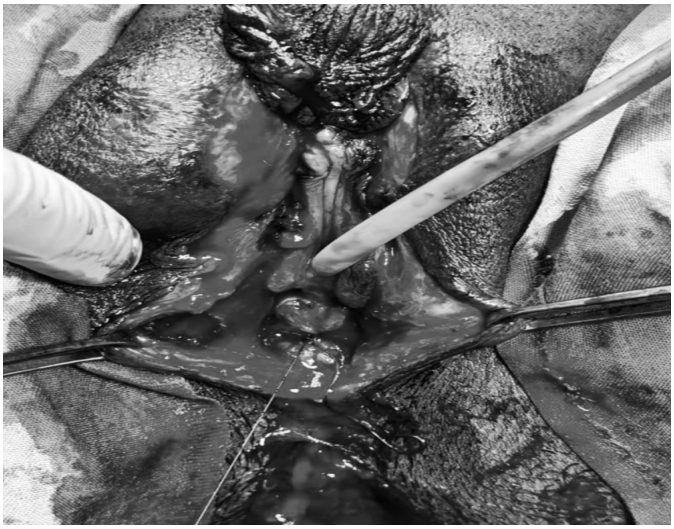
Patients with PGD presents with ambiguous genitalia due to testicular dysgenesis, ranging from either complete female phenotype with clitoris enlargement or normal male phenotype with hypospadiasis, cryptorchidism and micro penis.[6]

This is in discordance with our case where the patient had cryptorchidism, hypospadiasis, vaginal opening in perineum and absence of prostate. This again exemplifies the rarity of such a presentation.

The differential diagnosis of PGD includes Swyer syndrome (complete gonadal dysgenesis). Most cases of Swyer syndrome involve adults who are genetic males with 46XY karyotype but female external genitalia[3], but poorly developed secondary sexual characteristics; however, this patient had male external genitalia, which included a ventral urethral meatus along with a single vaginal sac. Notably, there were also no gonadal striae, or ovaries usually associated with either partial or complete gonadal dysgenesis, on further examination, thus highlighting the unique nature of this presentation.

Diagnosis and management of this case faced the challenges of diagnosing 46XY gonadal dysgenesis. The thorough assessment, including hormonal profile with imaging and genetic evaluation, made it possible to make a correct diagnosis, which directed the surgical procedure.[7] We performed surgical repairs in stages for this patient to address the topological abnormalities, but also maintaining focus on resolving functional and psychological issues. Comprehensive management was necessary for this patient to achieve an optimal outcome, and it required the integration of urology, endocrinology, and genetics services.[8]

Figure 2: During Surgery



The merits of this case are its unusual presentation as well as the literature gap in atypical presentations of 46XY DSD. This case underscores the importance of individualized, multidisciplinary care within their phenotypic spectrum, but all under a common genetic umbrella, unlike what has been so well documented before. Nevertheless, these data have limited external validity due to the absence of long-term follow-up data that are critical for functional, psychosocial, and surgical outcome assessment after such interventions.

This case adds to our existing body of literature by its illustration of the wide variation in presentation with 46XY DSD and the need for timely diagnosis and optimal management. By reporting this unusual

and atypical presentation of DSD, we hope to add to the evolving understanding of these lesions and their appropriate management.

CONCLUSION:

46XY DSD is a challenging but pertinent diagnosis to consider in the evaluation of patients with atypical genitalia and suspected disorders of sexual development, especially in a developing country like Pakistan such cases are often difficult to diagnose and manage due to limited diagnostic and treatment resources.[9] This case serves as an example of a systematic stepwise approach geared towards completion of genetic, hormonal, and imaging work-up to ascertain underlying etiologies to guide management. Timely diagnosis and an integrated approach to care, meeting the medical and psychosocial needs of these patients, are critical.[10] We report this rare presentation to raise awareness and add to a growing literature about the phenotypic spectrum of 46XY DSD. Continued research and clinical follow-up are needed to enhance outcomes and quality of life for at-risk individuals.

Declarations:

Ethics approval and consent to participate

Following local/national guidelines, ethical approval and written informed consent for case report studies are not required. The patient has provided written informed consent for the publication of the details of this medical case and any accompanying images.

Consent for publication

This report involves a case of medicine and the images, the patient gave written informed consent to publication of their case details.

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Competing interests

The author(s) declare that there is no conflict of interest regarding the publication of this article.

Data and materials availability

Original contributions presented in this study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

Supplemental Material:

Supplemental material for this article is available online.