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Case Series

Histopathological insights into dysgenetic gonads: A comprehensive case series analysis

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Abstract

Normal sexual development relies on the synergistic action of numerous activating and repressing factors interacting in a precise spatio temporal environment. Disorders of sex development (DSDs) can be classified into various categories, usually associated with abnormal development of chromosomal, gonadal, or anatomic sex. Females with DSDs can present with either ambiguous genitalia or with delayed puberty and infertility in later ages. Herein, we report all the dysgenetic gonads cases detected in our setting for a period of 5 years and discuss extensively on the same. This is a retrospective cross sectional study carried out in the histopathology section of Department of Pathology, SCB Medical College and hospital, Cuttack. The total duration of the study was 5years extending from June 2019-June 2024. All the histopathological confirmed cases of sertoli cell syndrome in clinically diagnosed 46 XY phenotypes was analysed. The radiological investigations like ultrasound where collected to confirm the same. We found a total of 10 patients diagnosed with sertoli cell only syndrome in clinically diagnosed phenotypic females. The mean age of patients was 21.11 years with age varying from 15yrs to 29 yrs. Testicular tissue structure identified showed hypospermatogonia with predominant sertoli cells and thickened basement membrane with interstitial leydig cell hyperplasia. Comprehensive evaluation, proper counselling to patients and their parents benefits from review of this information. Chromosomal karyotyping, microarray analyses, and next generation sequencing techniques are helpful to diagnose and identifies new genes involved. Multidisciplinary approach can help in surgery if given consent by the parents and the patient.

Keywords: Dysgenetic gonads, Karyotype analysis, Sertoli cells.

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1. Introduction

Normal sex development relies on the coordinated interplay of activating and repressing factors. The SRY gene on the Y chromosome triggers male sexual differentiation.[1] Disorders of Sex Development (DSDs) are a diverse group of congenital conditions marked by inconsistencies in the development of external and internal genitalia. DSDs can result from chromosomal defects, gonadal anatomy issues, or gonadal phenotype abnormalities. The incidence of DSDs ranges from 1 in 2,000 to 4,500 births.[2] While external genital ambiguity is typically identified at birth and further investigated, some individuals may only present in their second decade of life with symptoms such as delayed or absent puberty and infertility.

2. Materials and Methods

A retrospective cross-sectional study was conducted in the Department of Pathology at SCB Medical College and Hospital, Cuttack, over a five-year period from June 2019 to June 2024. The study focused on cases diagnosed with Sertoli cell-only syndrome in females, which represent dysgenetic gonads. Data were collected and analyzed based on sociodemographic characteristics. Comprehensive patient histories, clinical details, and biochemical investigation results, when applicable, were gathered and examined. Biopsy samples were fixed in 10% buffered neutral formalin overnight. Paraffin-embedded blocks were then prepared, and thin sections (4-6 µm) were cut using a microtome. These sections were stained with hematoxylin and eosin for histopathological examination under a microscope. Ethical

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approval for the study was obtained from the Institutional Ethics Committee of our institution. Additionally, relevant radiological investigations were reviewed and included from the case records maintained by the Department of Radiology.

3. Results

We found a total of 10 patients diagnosed with sertoli cell only syndrome in females clinically diagnosed as 46 XY DSD (disorder of sexual differentiation) as shown in **Table 1**. The mean age of patients was 21.11 years with age varying from 15 yrs to 29 yrs. Majority of the females presented with the chief complaints of failure to attain menarche, small underdeveloped breasts and some presented with mild lower abdominal pain despite being phenotypically female. Ultrasonography (USG) of inguinal region showed absence of uterus and ovaries with right deep inguinal ring showing a well-defined hypoechoeic space occupying lesion (SOL) of size 16x8mm, likely to be right testes. Similar hypoechoeic SOL of size 16x9mm is seen in left superficial inguinal ring along with another hypoechoeic SOL of size 27x14mm arising from its lower pole, likely to be neoplastic (**Figure 1**). Fine needle aspiration cytology (FNAC) is less invasive and gives informative data on spermatogenesis of the entire testes.[2] FNAC in few cases (**Figure 2**a, b) showed moderately cellular smears, with predominance of the presence of sertoli cells. Individual cells are medium shaped round cells, with scanty eosinophilic cytoplasm, having coarse clumped chromatin and only with few cells showing prominent nucleoli. However, there was absence of spermatogenic cells. Majority of cases in our setting had sent unilateral orchidectomy specimens to be examined. Case no. 5 and 10 showing bilateral involvement. After the tissues were sent for histopathological examination, diagnosis was confirmed as sertoli cell only syndrome, in all the cases with few cases like Case no.1 (**Figure 3**a,b),3,6,9 and 10 showing atrophic seminiferous tubules while the rest of the cases showed seminiferous tubules having thickened basement membrane (**Figure 4**a,b). All the cases showed leydig cell hyperplasia with none of them showing evidence of intratubular germ cell neoplasia or malignancy.

Table 1: Clinicopathological characteristics of dysgenetic gonads

Case. No.	Age	Gender	Gross findings (cut section)	Microscopy
1.	21 yr	Female	Testes with spermatic cord measuring 6cm in length. Testes measuring 3x1.7x1.2cm	Atrophic seminiferous tubules contain sertoli cells only. Interstitium shows leydig cell hyperplasia. No evidence of malignancy.
2.	29 yr	Female	Orchidectomy specimen measuring 5x4x3cm	Seminiferous tubules with thickened basement membrane with only sertoli cells. Focal leydig cell hyperplasia. No evidence of intratubular germ cell neoplasia or malignancy seen.
3.	18 yr	Female	Greyish brown globular tissue measuring 2.7x2.4x1.5cm, cut section showed greyish brown areas	Atrophic seminiferous tubules contain sertoli cells only. Interstitium shows leydig cell hyperplasia. No evidence of malignancy.
4.	29 yr	Female	Orchidectomy specimen with spermatic cord measuring 4.5cm in length	Testicular tissue showing seminiferous tubules containing rare primary spermatocytes and predominantly sertoli cells. No evidence of any neoplastic element seen.
5.	18 yr	Female	Received bilateral testes, right testes with epididymis measuring 5x4x1.3cm. Left testes with epididymis measuring 4x3x1.2cm	Testes structure identified showing hypospermatogonia with predominant sertoli cells. Thickened basement membrane. Focal interstitial leydig cell pseudohyperplasia seen.
6.	16 yr	Female	Orchidectomy specimen with spermatic cord measuring 5cm in length	Atrophic seminiferous tubules contain sertoli cells only. Interstitium shows focal leydig cell hyperplasia. No evidence of malignancy.
7.	22 yr	Female	Received greyish globular tissue labelled as right testes measuring 3.7x2.4x1.2cm, cut section showed greyish brown areas	Testes structure identified showing no spermatogonia except majority of sertoli cells. Focal thickening of basement membrane. Focal interstitial leydig cell hyperplasia seen.
8.	18 yr	Female	Testes with spermatic cord measuring 5.5cm in length. Testes measuring 3.2x1.8x1.5cm	Testicular tissue identified showing no spermatogonia except majority of sertoli cells. Focal thickening of basement membrane. Interstitial leydig cell hyperplasia seen.
9.	25 yr	Female	Orchidectomy specimen with spermatic cord measuring 5cm in length	Atrophic seminiferous tubules contains predominantly sertoli cells only. Interstitium

				shows focal leydig cell hyperplasia. No evidence of malignancy.
10.	15 yr	Female	Received bilateral testes, right testes with epididymis measuring 5.2x3.8x1.3cm. Left testes with epididymis measuring 4x2.5x1.2cm	Atrophic seminiferous tubules contains predominantly sertoli cells only. Interstitium shows leydig cell hyperplasia. No evidence of malignancy or intratubular germ cell neoplasia.

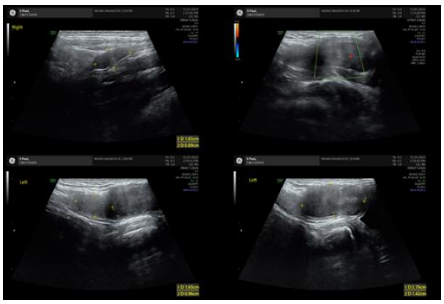

Figure 1: Ultrasonography of inguinal region shows absence of bilateral ovaries and uterus and presence of bilateral testis with a small focus of neoplastic pole on the left.

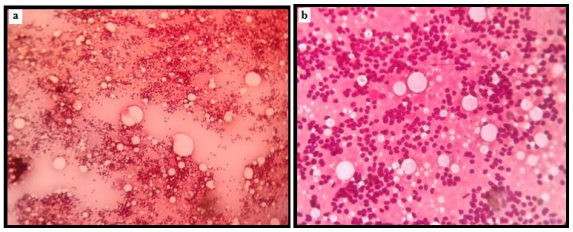

Figure 2: a, b: Cytosmear shows singly scattered sertoli cells only with absence of spermatogenic cells.

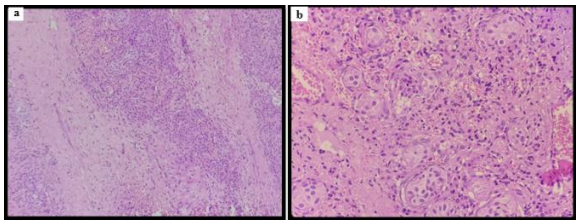

Figure 3: a, b: Case no 1: Microsection shows atrophic seminiferous tubules containing sertoli cells only. Interstitium shows leydig cell hyperplasia. No evidence of malignancy.

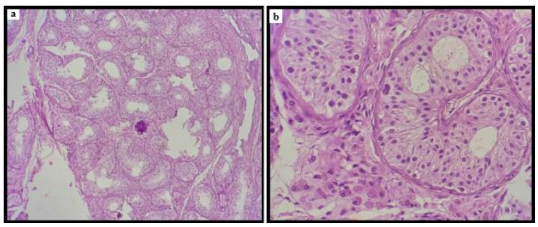

Figure 4: a, b: Case no.2: Microsection shows seminiferous tubules with thickened basement membrane predominantly with sertoli cells. Focal interstitial leydig cell hyperplasia. No evidence of intratubular germ cell neoplasia or malignancy seen.

4. Discussion

Disorders of sex differentiation constitutes a wide variety of congenital conditions caused due to chromosomal anomalies and gonadal anatomy abnormalities. DSDs are divided into various groups based on chromosomal anomalies. The first category of 46, XX DSD includes girls with a virilizing congenital adrenal hyperplasia and girls having abnormal ovarian development usually detected due to ambiguous genitalia. The second category of 46, XY DSD patients includes patients who present with abnormal testicular differentiation, defects in testicular biochemical parameters, and impaired testosterone function but predominantly show ambiguous genitalia. These group of patients may present with absence of development of female secondary sexual characters, delayed puberty and features of infertility in second decade of life due to absence of female internal genitalia. The third category includes the sex chromosome DSDs due to Turner Syndrome, Klinefelter Syndrome, and 45, X/46, XY gonadal dysgenesis. Turner syndrome patients having 45 XO phenotype usually presents with webbed neck and streak gonads. Klinefelter syndrome males with 47XXY phenotype may present with gynecomastia and smaller testicles. Other DSDs are the XX sex reversal, XY sex reversal, and ovotesticular disorders.[4] Mixed gonadal dysgenesis (MGD) represents a condition that falls between pure gonadal dysgenesis and ovotesticular-DSDs.[5] The external and internal genitalia, as well as the gonadal phenotype, can vary widely and is usually difficult to diagnose. However, the most frequently observed genotype in these individuals is 46XO/XX, though very rare cases of 46XY genotype has also been reported.[6]

46 XY DSDs. can be caused by different gene mutations during differentiation of testis, including mutations in SRY-box transcription factor 9 (SOX9), desert hedgehog signaling molecule (DHH), sex-determining region Y (SRY),[1] nuclear receptor subfamily 0 group b member 1 (NR0B1), nuclear receptor subfamily 5 group a member 1 (NR5A1), 7-dehydrocholesterol reductase (DHCR7), doublesex- and mab 3-related transcription factor 1 (DMRT1), Wilms' tumor suppressor gene 1 (WT1), and mitogen activated protein kinase 1 (MAPK3K1), CBX2, DHH, DMRT1, DMRT2, MAP3K1, and SOX8. Genetic mutations in the proteins required for testosterone biochemical synthesis are associated with the genes encoding SF1 (NR5A1), LH receptor (LHR), cholesterol desmolase (CYP11A1), 17α-hydroxylase/17,20-lyase (CYP17A1), steroidogenic acute regulatory peptide (StAR), 17β-hydroxysteroid dehydrogenase type 3

(HSD17B3), 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), 3α-hydroxysteroid dehydrogenase (AKR1C2/4), P450-oxidoreductase (POR), and 5α-reductase type 2(SRD5A2).[7,8] Genetic mutation involved in the interference of testicular action involves the androgen receptor gene (AR/NR3C4), located on Xq12 may present with labial masses, absence of uterus and ovaries leading to infertility along with phenotypically female characteritics.[9]

Microscopically, 46 XY DSDs who are phenotypically females but have male internal genital organs as seen in our cases usually show atrophic seminiferous tubules. Some cases show thickened basement membrane with persistence of seminiferous tubules with predominance of sertoli cells. Sertoli cells are characterized by round cells having centrally placed round nucleus, scant to moderate amounts of eosinophilic cytoplasm, fine paler chromatin with conspicuous nucleoli, extending as cytoplasmic projections in the seminiferous tubules. There is complete absence or partial presence of spermatogenic cells. Interstitial leydig cell hyperplasia also seen characterized by moderate to abundant amounts of eosinophilic cytoplasm. There is complete absence of female reproductive organs. It is equally important to look for evidence of malignancy as 46 XY DSDs show higher incidence of gonadoblastomas.[10] Gonadoblastomas detected in 30-75% of cases might show an increase evidence with advanced age.[11]

Biochemical hormones like LH, FSH and ultrasonography act as the adjuncts in making the diagnosis and plays a key role in diagnosing DSDs. Genetic mutation study of the above mentioned genes to recognize the cause of the disease gives positive result only in 43% of cases, wherein the SRY gene is identified as the most common amongst all the genes mutated. In our setting, due to lack of genetic study, the exact etiology of all the cases could not be carried out and were referred to higher centre.[12] Peripheral blood karyotype analyses for X and Y chromosomes, balanced translocation studies, fluorescence in situ hybridization (FISH) analysis, next generation sequencing (NGS) can be used to assess sex chromosome mosaicisms.[13]

While clinically diagnosing a patient with suspected dysgenetic gonads, it is important to respect the privacy and maintain confidentiality as this diagnosis in itself is very devastating to the caretakers. Social acceptance forms a core in adjustment with the society.

5. Conclusion

Dysgenetic gonads are variations in sex development that require a multidisciplinary approach. It's essential to provide patients and their families with thorough, age-appropriate medical information tailored to their developmental stage and cognitive abilities. Each case should be managed with respect, ensuring that the patient's quality of life is prioritized and meaningful.

6. Conflict of interest

None.

7. Source of Funding

None.

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