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Case Report

A case of partial androgen insensitivity syndrome: from diagnosis to management

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ABSTRACT

Partial androgen insensitivity syndrome (PAIS) is a rare 46XY disorder that results from mutations in androgen receptors leading to failure of normal masculinization of external genitalia in genetically male individuals. An 18-year-old female visited our OPD i/v/o not attainment of menarche, on examination minor virilization of voice, bilateral inguinal masses, poorly developed labia majora, clitoromegaly, blind vaginal pouch was noted. Imaging showed absent mullerian structures with bilateral ectopic testes with overall features of partial androgen insensitivity syndrome. Karyotyping showed 46XY. PAIS can be presented as ambiguous genitalia at birth or as predominant female to male phenotype with varying degrees of virilization. Early identification and multi-disciplinary management aiming at appropriate gender assignment, gonadectomy, reconstructive surgery, hormone replacement therapy and screening of other family members should be done.

Keywords: Partial androgen insensitivity syndrome, Disorder of sexual development, Virilization, Gonadectomy, Hormone replacement therapy

INTRODUCTION

Partial androgen insensitivity syndrome (PAIS) is a rare X-linked recessive condition resulting from partial inability of cells to respond to androgen.[1] Partial responsiveness of the cell to androgen hormone impairs the masculinization of male external genitalia as well as development of secondary sexual characteristics at puberty, leading to spectrum of phenotypic variations in individuals with 46 XY karyotype.[2] The spectrum of clinical presentation may vary from ambiguous genitalia at birth, adult female phenotype females with mild virilization to under virilized male who may be fertile or infertile even within one affected family.[3,4] Management should be done by multidisciplinary approach aiming at appropriate sex assignment, psychological support, removal of undescended testes, hormone therapy and reconstructive surgery when needed.[5] This case study aims to illuminate regarding the clinical manifestations, diagnostic challenges and therapeutic considerations associated with PAIS contributing to a better understanding of this complex condition.

CASE REPORT

An 18-year-old female visited our OPD i/v/o not attainment of menarche. No significant past medical and surgical history, however history of primary infertility was present in maternal aunt.

On examination patient was tall with height of 170 cm, virilization of voice was present. Her sexual maturity rating was breast – stage 2 (Figure 1), pubic hair – stage 4 (Figure 2) and axillary hair – sparse. CVS and RS examination was normal. Per abdomen - B/L freely mobile inguinal mass of 3×2 cm on right side and 2×2 cm on left side and cord structures palpable which were suggestive of testes. Perineal examination revealed poorly developed labia majora, prominent clitoris of 1cm suggestive of clitoromegaly (Figure 3) and short vagina of 3.5 cm with a

blind ended pouch with absent cervix was noted. Rectal examination revealed absent uterus.

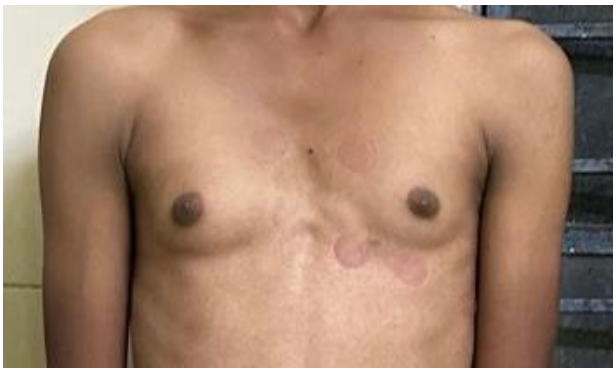

Figure 1: Breast – stage 2.

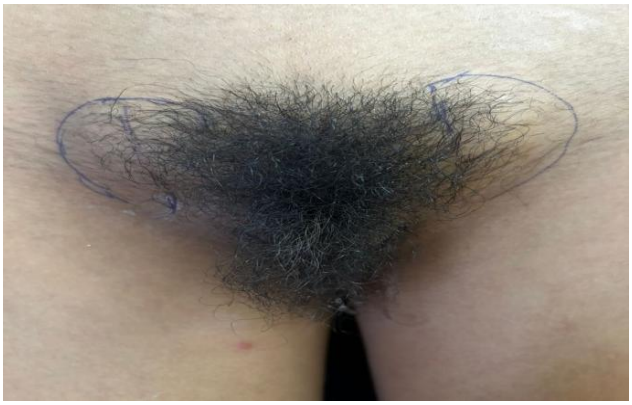

Figure 2: Pubic hair – stage 4.

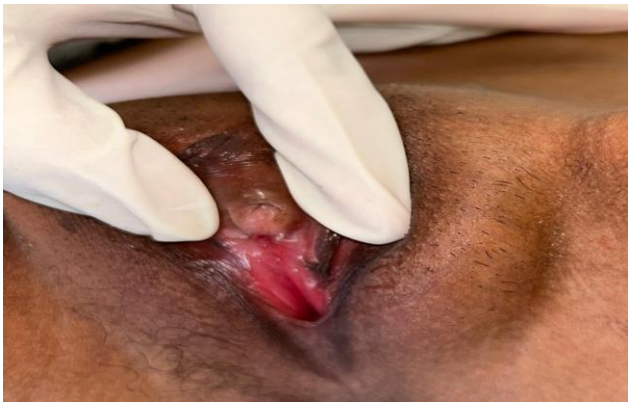

Figure 3: Poorly developed labia majora, prominent clitoris of 1cm

In view of above history and clinical findings, sexual development disorder was suspected and investigations were ordered for same: haemoglobin – 12.9 mg/dl, RBS – 98 mg/dl, TSH – 2.86 microIU/ml, FSH – 9.36 mIU/ml, LH-13.5 mIU/ml, prolactin – 7.71 ng/ml, estradiol – 33.80 pg/ml, testosterone – 115.03 ng/dl; LFT, RFT, serum electrolytes, coagulation profile, ECG and ECHO normal; and USG abdomen and pelvis – normal abdomen study. Uterus and ovary are streaky and not well made out.

MRI

E/o well defined ovoid structure which is T2/SPAIR hyperintense and T1 isointense noted in right inguinal region of 2×2.1×1.4 cm and left side of labia majora 0.7×1.7×3 cm suggestive of B/L small ectopic testes, also a tubular cord like structure seen arising from cranial aspect of B/L ectopic testes S/o spermatic cords: absence of Mullerian structures, presence of lower vagina 35 mm; clitoral hood length 8.4 mm, clitoral glans width 5.4 mm, clitoral index 44 mm^2 s/o clitoromegaly; and overall F/S/O partial androgen insensitivity syndrome.

Management

Patient and attendees were counselled about the present condition, social implications and probable complications of the same. Since patient was being raised as female and was willing to continue as the same, after taking informed written consent B/L gonadectomy was performed by surgeons' team under spinal anaesthesia to prevent development of gonadal malignancy (Figure 4) and specimen was sent for HPE.

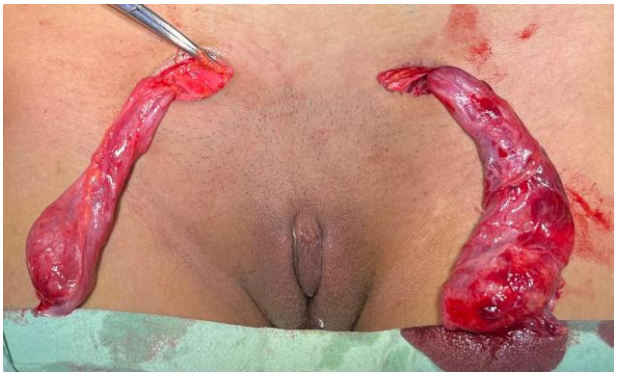

Figure 4: Gonadal malignancy.

HPE report – left and right gonad testicular tissue with seminiferous tubules showing maturation arrest. Johnson score for spermatogenesis – score 3 (Figure 5).

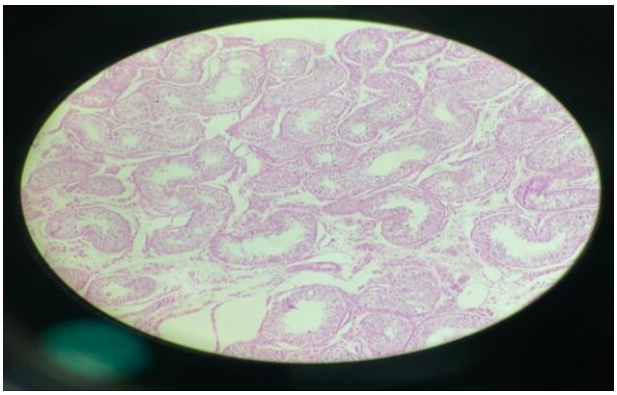

Figure 5: HPE report.

DIAGNOSTIC REPORT

agilus diagnostics

REF. DOCTOR : SELF

CODE/NAME & ADDRESS :C000030417
HI TECH CLINICAL LABORATORY
#1991, 1ST FLOOR, ASHIRWAD, P. J. EXTN.,
DEVANGERE 577004
8192272606 9986044674

ACCESSION NO : 0081XI015834
PATIENT ID : CHOWF19090681
CLIENT PATIENT ID: C438484
ABHA NO :

AGE/SEX :18 Years Female
DRAWN :18/09/2024 00:00:00
RECEIVED :19/09/2024 13:41:08
REPORTED :04/10/2024 17:51:00

Test Report Status Final	Results	Units

CYTOGENETICS

BLOOD LYMPHO CULTURE

SPECIMEN	WHOLE BLOOD
INDICATIONS	H/O PARTIAL ANDROGEN INSENSITIVITY SYNDROME
CELLS COUNTED & ANALYSED	20
CELLS KARYOTYPED	08
KARYOTYPE	46,XY in a phenotypic female

METHOD : KARYOTYPING

Comments

KARYOTYPE: 46,XY in a phenotypic female

DIAGNOSIS: ABNORMAL KARYOTYPE CONSISTENT WITH XY PHENOTYPIC FEMALE

INTERPRETATION:

Chromosomal analysis (GTG-Banding with 500 band resolution) following stimulated cell culture techniques revealed 46,XY male pattern in all the metaphases analysed. In a phenotypic female, this finding is consistent with androgen insensitivity or gonadal dysgenesis.

This abnormality could be due to submicroscopic chromosomal deletions or duplications, steroid biosynthetic defects, androgen insensitivity syndrome or gonadal dysgenesis or an inherited chromosome with a deletion of the SRY gene, or other syndromes associated with somatic anomalies. A deletion or point mutation of the SRY gene accounts for 20-30% of the XY female cases. Phenotypic females with this karyotype are at increased risk for gonadal tumor; a thorough evaluation is suggested, if not already performed.

Figure 6: Test report.

Oral estrogen replacement therapy was started at discharge.

Patient was also counselled regarding menstruation, fertility issues and was advised to undergo vaginoplasty once she decides to be sexually active.

Evaluation of siblings and genetic counselling was advised but was denied due to financial constraints.

DISCUSSION

Androgen insensitivity syndrome (AIS) was first described in detail by Morris, at Yale, who coined the name "testicular feminization syndrome" in 1953.[6] This XY disorder of sexual development (DSD) results from mutations in the androgen receptor (AR) gene located on the X chromosome (Xq12) and therefore follows an X linked recessive pattern of inheritance.[7] More than 800 different AR mutations, which is nuclear transcription factor has been identified which therefore can produce a variety of phenotypes in males having normal testes and testosterone production.[8] On one end of this spectrum is total lack of response to androgens as seen in CAIS who are XY genotypically and are usually tall phenotypic females with well-developed breasts, blind vagina and absent or scanty pubic and axillary hair, and in the other end is an infertile male or minimal AIS where the patient is phenotypically male with sterility, gynaecomastia and azoospermia. PAIS is in the middle of spectrum, which is the most challenging to diagnose early and presents as diagnostic dilemma.

PAIS is an X linked recessive disorder results from a milder AR mutation; phenotypic presentation can vary from ambiguous genitalia to nearly normal male. The prevalence of PAIS is estimated to be 1 in 20,000 to 1 in 64,000 males, while incidence is 1 in 1,30,000 births.[9] The estimated incidence of CAIS is 1 in 20,400 XY births.[10]

The phenotypic spectrum of androgen insensitivity syndrome is described in Figure 7.

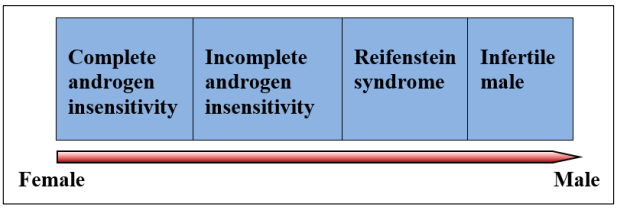

Figure 7: Phenotypic spectrum of androgen insensitivity syndrome.

The receptor defect results in insensitivity to androgen. Consequently, androgen induced wolffian duct development cannot proceed normally. The presence or absence of wolffian duct derivatives like epididymis, vas deference varies with the type of mutation. In case of point mutations remnants can be observed, whereas in case of premature stop codons or frameshift mutations, wolffian structures are completely absent.[11] In the presence of Y chromosome, gonads are testes, which produce normal amounts of AMH, which effectively suppress mullerian duct development. Therefore, the uterus and fallopian tubes are typically absent as seen in our patient, although vestiges are observed in few case reports.[12] The testes are most commonly located in inguinal canals or in the labia majora due to their descent from abdomen mediated by AMH, which is also seen in our case. The external genitalia range from typical female to male based on severity of insensitivity. The vagina is blind or short reflecting only the contribution from urogenital sinus. Axillary and pubic hair are absent in case of complete androgen insensitivity syndrome (CAIS), scant or well developed in PAIS depending on the spectrum. Moreover, as estrogen is produced by the aromatization of testosterone, such individuals manifest thelarche, which is exhibited by our patient too. The overall body habitus also is a female. However, they can virilize or feminize at puberty.

Diagnosis of AIS is usually made in four scenarios. First in fetal life if karyotyping 46XY, does not match with prenatal female sex USG feature (not routinely done unless indicated), secondly presence of ambiguous genitalia at birth, thirdly during childhood when a girl presents with inguinal hernia and lastly in adolescents in puberty presenting with primary amenorrhea as seen in our patient. Inguinal hernias are uncommon in females and the incidence of AIS range from 0.8% to 2.4% in their presence. Our patient presented to us in adolescence with complaints of primary amenorrhea had a female external phenotype and was diagnosed incidentally as PAIS by noting the minor virilization of voice, external genitalia which revealed clitoromegaly on examination, absent mullerian structures in imaging and presence of cryptorchid testes with spermatic cords.

An individual with 46XY karyotype is diagnosed with PAIS- phenotypic women with mild virilization if they have following characteristics: primary amenorrhea with normal body hair, normal axillary, pubic hair and breast development, undescended testes in inguinal region or in

labia majora, external genitalia exhibiting partial fusion with or without clitoromegaly, blind ending vagina, absent mullerian structures, underdeveloped or absent male internal genitalia, histology of testes showing normal or increased number of Leydig cells and absent spermatogenesis, normal or moderately increased testosterone, raised LH levels resulting from negative feedback effects of androgens at hypothalamic-pituitary level. However, the most reliable method for diagnosis is to sequence the AR gene using DNA with reference to database that lists all the mutations.

All the above-mentioned characters are present in our case with mild virilization of voice, however AR gene sequencing was not done due to financial constraints.

The close differential diagnosis for our case was steroid 5 alpha reductase deficiency however absent Wolffian duct derivatives and presence of breast in our case excluded this condition and hence ratio of testosterone to DHT was not done.

Another differential was defect in testosterone biosynthesis, however normal to high serum testosterone concentration excluded the diagnosis. The last differentials were mixed gonadal dysgenesis who often have a single descended gonad or exhibit some phenotypic features of turner syndrome was absent in our case. Hence the diagnosis of partial androgen insensitivity syndrome was made.

The clinical management of PAIS depends on the severity of the androgen signaling defect and the individual's specific needs and was directed towards the following.

Appropriate gender assignment – it is a psycho social emergency and should be done at birth or as soon as it is detected based on patient's needs and desires.

Psychological support – truthful education and psychological support can help individuals with PAIS to cope with emotional and social challenges.

Surgery - gonadectomy to prevent tumourogenesis in cryptorchid testes. In contrast to CAIS where gonadectomy is best postponed until after puberty is completed, in PAIS it is done earlier to prevent virilization at puberty[13] and hence was performed as soon as diagnosis was made in our case.

Hormone therapy - oral estrogen was started soon following surgery in our case.

Genetic counselling – it is recommended for patient and family members which provides information about disorder, its genetic basis, risk of recurrence. It can also confirm the diagnosis and identify specific mutation.

Reconstructive surgery – vaginal reconstruction was advised for our patient in later dates when she is ready to start sexual activity.

CONCLUSION

AIS, though rare, is one of the common types of XY DSD with wide spectrum ranging from complete female phenotype to male phenotype with infertility. Understanding the genetic basis and the impact of mutation on androgen signaling is crucial for providing accurate diagnosis, specific treatment and informed genetic counseling. Ideally most cases of PAIS should be raised as males but if as in our case was raised as female with milder form of spectrum, a multidisciplinary approach with tailor made decision is crucial to provide best prognosis for satisfaction of patients and their attendees.

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Ethical approval: Not required

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