

# Androgen Insensitivity Syndrome: A Rare Cause of Primary Amenorrhoea

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## ABSTRACT

Androgen Insensitivity Syndrome (AIS) is a rare X-linked Disorder of Sexual Differentiation (DSD) caused by a mutation in the Androgen Receptor (AR) gene, which is located on the X chromosome (Xq11-q12). It can present with a wide spectrum of phenotypes depending on different mutations of the AR gene. It is classified into mild, partial, and complete AIS. In this series of cases, authors describe patients who presented to tertiary hospitals over several years. Case 1 presented with inguinal masses and primary amenorrhoea, which upon investigations revealed complete AIS. Case 2 was a young child who underwent surgery for an inguinal hernia, and later histopathology and karyotype revealed a diagnosis of complete AIS. Case 3 presented with large adnexal masses to oncology, where intraoperatively absent Mullerian structures, histopathology, and karyotype gave the diagnosis of Complete AIS. Case 4 presented with hirsutism, primary amenorrhoea, and clitoromegaly. Upon investigation, imaging and karyotype with virilising features led to the diagnosis of partial AIS. The absence of Mullerian structures on imaging, chromosomal analysis, and the finding of undescended testicular masses in inguinal regions clinch the diagnosis. These patients should undergo gonadectomy after puberty to decrease the chances of malignancy. Therefore, when investigating the cases of primary amenorrhoea, patients with absent pubic/axillary hair and absent uterus/ovaries should raise suspicion of AIS. Also, any young female child with an inguinal hernia should be investigated for AIS.

**Keywords:** Androgen receptor gene, Case series, Disorder of sexual differentiation, Karyotype, Phenotypical sex, X- linked disorder

## INTRODUCTION

The AIS is considered a disorder that causes resistance to androgen actions due to X-linked mutations in the AR gene [1]. It expresses a variety of phenotypes ranging from infertile males to phenotypical females with primary amenorrhoea depending on the severity of androgen resistance. These patients mostly present with primary amenorrhoea during pubertal age or as young girls with inguinal swellings which are misdiagnosed as inguinal hernias [1]. It is an uncommon disorder, and therefore, diagnosis may sometimes be delayed. Peripheral aromatisation of testosterone leads to oestrogen formation and thus normal breast development in these cases. The testicular masses, if not removed after puberty, may lead to malignant transformations [1].

## CASE SERIES

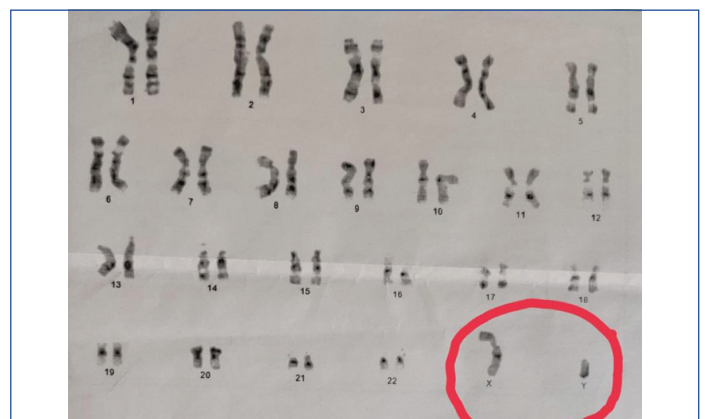
### Case 1

A 20-year-old girl presented with a history of not attaining her menarche yet. She was referred from the Surgery Department while being investigated for bilateral inguinal hernia. On examination, she had normal female facial features. Her height was 160 cm. She had normal breast development (Tanner 4) [2] and absent/sparse pubic and axillary hair. Her external genitalia were normal with a blind vagina of approximately 4 cm (which was examined under anaesthesia). She also had globular masses in bilateral inguinal areas with a clinical diagnosis of bilateral inguinal hernias. Her pelvic sonogram showed an absent uterus and ovaries. The Magnetic Resonance Imaging (MRI) pelvis confirmed the Ultrasonography (USG) diagnosis, but there was no mention of ectopic gonads. A repeat USG of the inguinal region suggested hypoechoic well defined structures in relation to superficial inguinal rings suggestive of testicular masses. Her hormonal assays showed normal Luteinising Hormone (LH), Thyroid Stimulating Hormone (TSH), and prolactin. Serum testosterone level was 1293 ng/dL, and

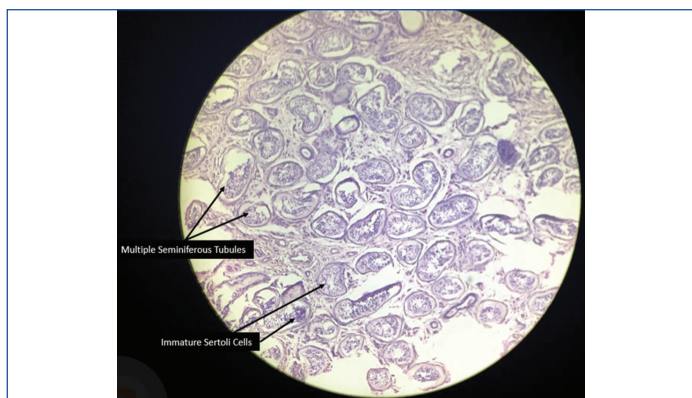
Antimullerian Hormone (AMH) values were 12 ng/mL [Table/Fig-1]. The karyotype showed a genotype of 46 XY [Table/Fig-2]. No family history of primary amenorrhoea was present. She underwent a bilateral gonadectomy via the inguinal approach by a urologist. Her histopathology showed benign testicular tissue and seminiferous tubules with maturation arrest of spermatogonia [Table/Fig-3]. The patient is presently on oestrogen replacement therapy and calcium supplementation. She is undergoing psychological counselling. Options of vaginal dilatation/vaginoplasty have been explained to the patient. A diagnosis of complete AIS was made.

Investigations	Case 1	Case 2	Case 3	Case 4	Normal range
LH	4.9	2.1	4.8	4.09	1.2-7.8 IU/mL
Total testosterone	1293	10.1	988	838	300-1000 ng/mL
Antimullerian hormone	12	4	8	5	1-3 ng/mL
TSH	3.4	2.4	4.3	3.2	0.5-5.0 mIU/L
Karyotype	46 XY	46 XY	46 XY	46 XY	

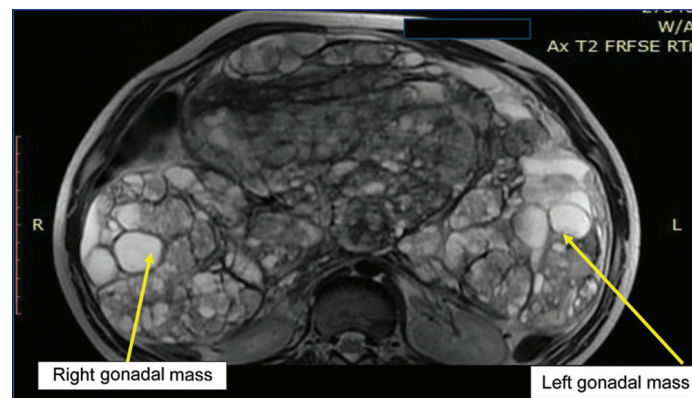
[Table/Fig-1]: Hormonal assays and karyotype reports.



[Table/Fig-2]: Karyotype of patient-46 XY (Case1).



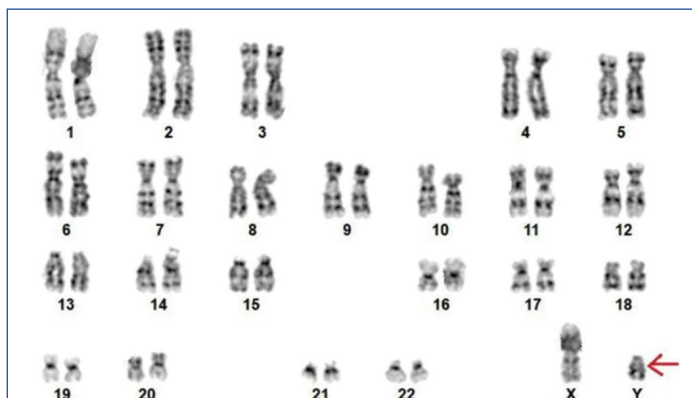
**[Table/Fig-3]:** (Case 1) Histopathology showing multiple seminiferous tubules with maturation arrest of spermatogonia. No evidence of atypia or malignancy.



**[Table/Fig-5]:** MRI image showing bilateral large mass lesions (Right 25×21×13.2 cm) (Left 15×13.8×10.9 cm) (Case 3).

**Case 2**

An eight-year-old girl child presented to Surgical Outpatient Department (OPD) with bilateral inguinal masses, which had been observed by her mother since birth. She underwent surgery with the initial diagnosis of an inguinal hernia, but it was discovered intraoperatively that the masses were testicular in nature, characterised by high vascularity and haemorrhage. Due to severe bleeding, the bilateral inguinal masses were excised, and histopathology confirmed the presence of benign testicular tissue. A diagnostic laparoscopy performed simultaneously revealed an absent uterus and adnexa. Despite having normal external female genitalia and a blind vagina, the karyotyping confirmed a 46 XY genotype [Table/Fig-4]. Her testosterone levels were consistent with those a male child, while the rest of her hormonal profile was normal for her age [Table/Fig-1]. She was scheduled for oestrogen therapy during puberty to facilitate breast development. Her parents have received psychological counselling regarding raising her as a girl child. A diagnosis of complete AIS was established.



**[Table/Fig-4]:** Karyotype of patient 46 XY (Case 2).

immature testicular teratoma grade 3 (T1a;N0;Mx). Postoperatively, she received six cycles of chemotherapy. Currently, the patient is undergoing oestrogen replacement therapy along with calcium supplementation. A diagnosis of complete Androgen Insensitivity Syndrome (AIS) with testicular teratoma was made.

**Case 4**

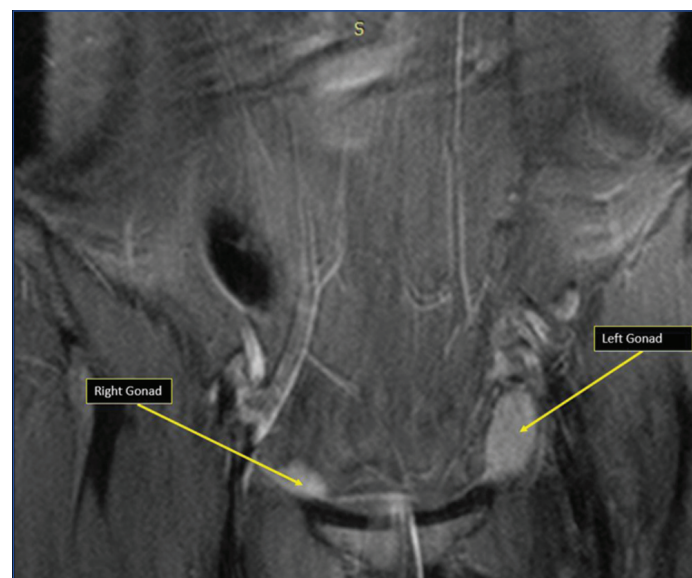
A 22-year-old woman presented to the Gynaecological OPD with a history of not having attained menarche and hirsutism. She had facial and chest hair that she had been shaving regularly once every two weeks for the last 6-7 years (Ferriman-Gallwey score: 14). There was no similar history in her sisters. Upon examination, she had normal pubic and axillary hair. Her height was 162 cm. She had acne and coarse hair on her face. Breast development was Tanner stage 3. Pubic and axillary hair were Tanner stage 4. During abdominal examination, non tender globular masses (4x3 cm) were felt in the inguinal regions bilaterally. Genital examination revealed clitoromegaly and a blind-ending vagina. An ultrasound showed an absent uterus and adnexa, with hypoechoogenic masses in the inguinal canal suggestive of bilateral undescended testes. Subsequent MRI confirmed these findings [Table/Fig-6]. A karyotype revealed 46 XY. She underwent bilateral orchidectomy [Table/Fig-7] and herniorrhaphy. The histopathology report showed benign testicular tissue. A diagnosis of partial AIS was made. The patient is currently on oestrogen replacement therapy, calcium supplementation, and receiving psychiatric counselling.

**DISCUSSION**

The AIS is a rare type of DSD in which the genetic sex and phenotypical sex are atypical. It is an X-linked recessive genetic

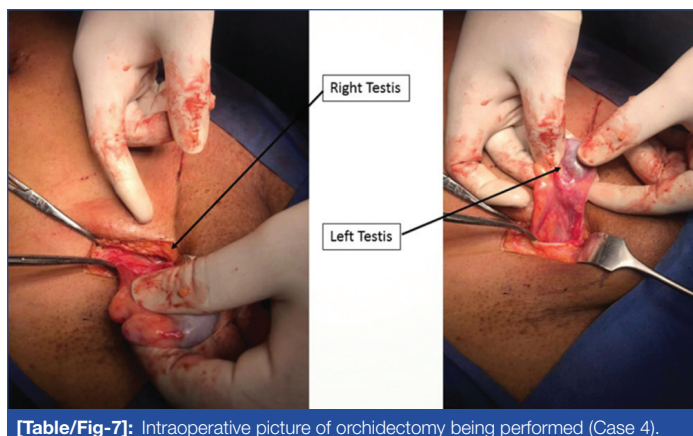
**Case 3**

A 19-year-old girl from a tribal location was referred to the Oncology department with a history of abdominal fullness and intermittent pain over the past three months. She reported not having reached menarche yet. Upon examination, she displayed a normal female phenotype, a height of 163 cm, Tanner stage 4 breast development, sparse pubic/axillary hair, and essentially normal external genitalia with a blind vaginal pouch measuring 3-4 cm. An abdominal ultrasound revealed suspicious complex adnexal masses, while pelvic MRI showed an absent uterus with large adnexal masses, ascites, and multiple peritoneal deposits [Table/Fig-5]. Karyotyping revealed a 46 XY genotype. Her hormonal profile was normal [Table/Fig-1]. Tumor marker levels were as follows: Ca 125: 15 U/mL (<35), Carcinoembryonic antigen: 2.3 ng/mL (<3), CA 19.9: 5 U/mL (<37.0), Alpha-Fetoprotein (AFP): 158 ng/mL (<9), LDH: 693 U/L, and Beta HCG: 1.2 mIU/mL (<2). She underwent exploratory laparotomy with excision of lesions, omentectomy, and pelvic lymph node dissection. Histopathology results indicated an



**[Table/Fig-6]:** MRI image showing bilateral testes in inguinal canal (Case 4).





**[Table/Fig-7]:** Intraoperative picture of orchidectomy being performed (Case 4).

disorder with an incidence of 1 in 20,000 to 100,000 births [1]. The Office of Rare Diseases of the National Institutes of Health classifies AIS as a rare disease [3]. It is mainly linked to a mutation in the AR gene (Xq11-q12) [4]. This mutation leads to a person with a 46 XY genetic makeup being resistant to androgens. Subsequently, a spectrum of changes occurs depending on the severity of androgen resistance. Patients can present variably, from infertile males to a full female phenotype like present study patients [5,6]. It was first described by John Morris [6].

In the embryo, the AR gene is expressed from eight weeks of gestation, and the male testis in utero stimulates the normal differentiation of the Wolffian duct system into the epididymis, vas deferens, and seminal vesicles. Dihydrotestosterone usually stimulates the formation of male external genitalia [7]. However, due to end-organ resistance to testosterone in AIS, there is an absence of Wolffian duct derivatives and the prostate. Feminine external genitalia are seen due to absent androgenic actions. The Y chromosome causes the gonads to develop as testes, which remain undescended. Due to AMH-mediated descent of the testes, they may be found anywhere along their path of descent (mostly in the inguinal canal) [7,8]. Due to the inhibitory actions of AMH in utero (7<sup>th</sup> week) (produced by Sertoli cells of the testes), there is an absence of the proximal vagina, cervix, uterus, and fallopian tubes too. The lower blind-ending vagina, which is present in such patients, is derived from the urogenital sinus. This is how present study patients were found clinically.

There are predominantly three categories of AIS [8,9]. Firstly, Mild AIS (MAIS) presents as a male phenotype with impotence, infertility, and gynecomastia. Secondly, Partial AIS (PAIS) usually has a spectrum of presentations depending on the amount of virilisation, ranging from a female phenotype with mild clitoromegaly to a male phenotype with peripheral hypospadias, bifid scrotum, and micropenis. Thirdly, Complete AIS (CAIS) presents with a female phenotype with primary amenorrhoea, absent/sparse axillary/pubertic hair, normal breast development, and inguinal swellings. Endocrine features of CAIS at puberty show elevated LH and serum testosterone due to androgen insensitivity and consequent lack of negative feedback exerted on the hypothalamus and pituitary [9]. First three cases were Complete AIS, and the fourth one, which had features of virilisation, was diagnosed as Partial AIS.

The abundant conversion of androgens to oestrogen peripherally by P450 Aromatase leads to the spontaneous development of the breast and a typical growth spurt during puberty. Due to the presence of the Y chromosome, they are taller than the average girls [9]. All index patients had normal breast development and were taller than the average girls. Usually, patients get diagnosed at three stages of life: First during puberty with a history of primary amenorrhoea with normal breast development and absent pubic/axillary hair; Secondly as small kids with inguinal swellings with an erroneous diagnosis of inguinal hernia [10]; Thirdly, they may also

be diagnosed rarely, very early at the neonatal stage if there was a mismatch between amniocentesis which reported 46 XY karyotype, and at birth female external genitalia was observed. Guo M et al., Shrestha A et al., described patients with CAIS who had erroneously undergone surgery for inguinal hernia in childhood before getting a correct diagnosis [10,11] like the second case of present series.

The management protocol mainly consists of gonadectomy, vaginal dilatation/plasty, oestrogen and calcium replacement, and psychiatric counselling. Orchidectomy is usually not recommended in childhood because the testosterone will help in breast development and height spurt during puberty. The intra-abdominal testis makes such patients prone to gonadal cancer [12]. So, after the pubertal growth is over, it is recommended that they undergo gonadectomy. Compared with CAIS patients, PAIS patients present a higher risk of developing testicular tumors. AIS patients present a high-risk of developing osteoporosis, cognitive decline, and cardiovascular disease if the oestrogen deficit is not compensated [13]. All present series cases except the second underwent orchidectomy after puberty.

Whole-Exome Sequencing (WES) is one of the most valuable tools for the detection of CAIS and its mutations [13]. Carrier testing is recommended within the family because the disease shows familial tendencies. Carrier females have a 50% chance of transmitting the mutated AR gene in each pregnancy. AIS has been described among siblings by Jiang Lu et al., and Shankar A et al., [9,12]. Psychosexual identification poses a challenge for these patients. They are more susceptible to developing anxiety, depression, and other psychiatric conditions. Acceptance of infertility is a major source of distress for them. Comprehensive psychiatric assessment and counselling can significantly help alleviate distress and improve their quality of life [14,15].

## CONCLUSION(S)

The AIS is a rare DSD caused by androgen resistance, resulting in varied clinical presentations. Patients require orchidectomy after puberty. Every female child with an inguinal hernia needs evaluation for AIS to prevent erroneous surgeries. Hormone replacement therapy, gender assignment surgeries, and strong psychiatric support are long-term goals for improving the quality of life for these patients.

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