

# A Case of Androgen Insensitivity Syndrome with Intraabdominal Testes in a 62 year old Woman

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Androgen Insensitivity Syndrome (AIS) is a disorder wherein a patient presents with a female phenotype but is actually genetically male with an XY karyotype. Typically, AIS is diagnosed at the beginning of second decade, when a phenotypically female patient complains of amenorrhea. It is extremely rare to make a first diagnosis of AIS after the fifth decade of life. This case report presents a 62-year old female who consulted because of primary amenorrhea and intraabdominal mass. Patient was diagnosed with Complete Androgen Insensitivity Syndrome based on physical exam findings, imaging studies, endocrine tests and karyotyping. She underwent exploratory laparotomy, adhesiolysis and bilateral orchiectomy. This report will discuss diagnosis and appropriate management of patients with Complete Androgen Insensitivity.

**Key words:** Androgen Insensitivity Syndrome, intraabdominal testes

## Introduction

Androgen insensitivity syndrome was originally termed testicular feminization. This syndrome was first described by Morris after reviewing 80 cases in 1953.<sup>1</sup> These patients, despite having a male genotype, present as asymptomatic, functionally normal but reproductively sterile females. The woman is a phenotypically normal female with well-developed breasts, normal external genitalia, a vagina that ends with a blind pouch, no uterus and sparse or absent pubic hair and axillary hair. The testes may be located either in the inguinal or abdominal region and can be associated with benign and malignant tumors. The prevalence of AIS is between 1/20,000 and 1/60,000 in genetic males.<sup>2</sup> Presented is a case of a 62-year old female with complete androgen insensitivity syndrome who presented with primary

amenorrhea and a tumor in her resected gonads. Appropriate management for this disorder is also discussed.

## The Case

This is a case of R.R, a 62 year old female, married, retired elementary school teacher who consulted at the outpatient department with a chief complaint of hypogastric pain of two months duration.

The patient did not have her menstrual period since she reached pubertal age. The patient noted breast development at age of 13, but with absence of axillary hair. She consulted for primary amenorrhea when she was 25 years old. An ultrasound was done but patient could not recall the results. No further work-ups and interventions were done.

Two months prior to consult, patient experienced intermittent, mild to moderate, non-radiating, hypogastric pain, associated with pressure on the hypogastric area and polyuria. She consulted at a local health center where she was treated for urinary tract infection. She was given unrecalled antibiotics which failed to improve her symptoms, prompting her to seek consult at a regional hospital. Whole abdominal ultrasound was done which revealed nephrolithiasis, left pelvic mass, probably ovarian new growth. Patient was referred to this institution for further evaluation and management.

The patient is not a known diabetic, hypertensive and asthmatic. She is allergic to chicken and Amoxicillin. She has no previous history of hospitalizations nor surgeries.

The patient has a family history of hypertension on her maternal side. She is the third among five siblings with an older sister who also had primary amenorrhea. Her mother's prenatal course was unknown. There were no congenital malformations noted at birth. Patient had no developmental delays.

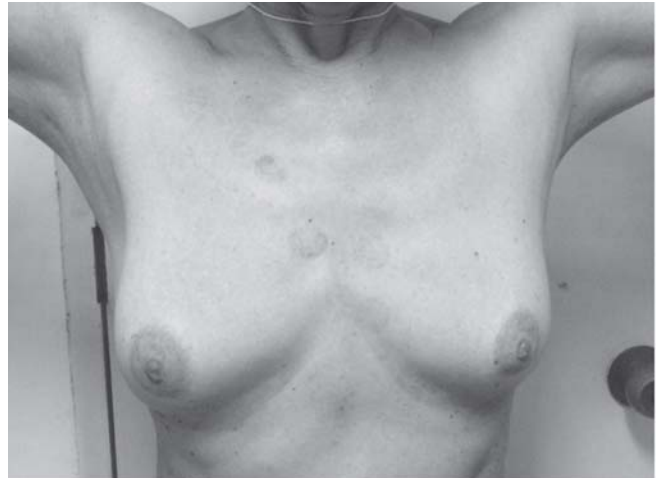
Patient experienced thelarche at 13 years old. Patient is a nulligravid, no menarche. She had her first sexual intercourse at age 28 years old, with one lifetime partner. The patient is married for 32 years. She denied history of neither dyspareunia nor post coital bleeding. Patient had no history of oral contraceptive pills usage. She had no pap smear done.

The patient is a college graduate with a Bachelor's degree in Education. She is a non-smoker and non-alcoholic beverage drinker. She denies use of any illicit drugs.

On physical examination, patient was conscious, coherent and ambulatory, with stable vital signs. Patient weighed 51 kg., with a height of 158 cm (BMI of 20.48 kg/m<sup>2</sup>). Patient appeared phenotypically female with normal built for her age (Figure 1). Her skin was soft and smooth. Breasts were symmetrical, areola and papilla form a secondary mound above level of breast (Tanner Stage 4). No breast mass nor lesions, no nipple discharge (Figure 2). The axillary area was smooth with no axillary hairs noted (Figure 3).



**Figure 1.** Index patient with normal habitus, phenotypically female.



**Figure 2.** Index patient with Tanner stage 4 breast development.



**Figure 3.** Index patient with absent axillary hair.

The abdomen was flat, soft, with normoactive bowel sounds. There was a movable, non-tender, cystic mass, measuring 8cm x 6cm. The upper and lower extremities appeared normal, no deformities. On pelvic examination, the external genitalia was grossly normal. There was sparse growth of long, thin, straight, slightly pigmented pubic hair along mons pubis and labia majora (Tanner stage 2) with presence of a vaginal orifice. No lesions were noted (Figure 4). On speculum exam, there was a smooth vaginal wall, blind pouch, and no cervix was visualized. There were no masses, lesions, erosions, discharges, nor bleeding noted. On internal examination, the vaginal canal measured 6cm in length and ends in a blind pouch. No palpable cervix, uterus, adnexal mass were noted. On rectovaginal examination, there was tight rectal sphincteric tone, normal rectal mucosa. No rectal masses nor tenderness.



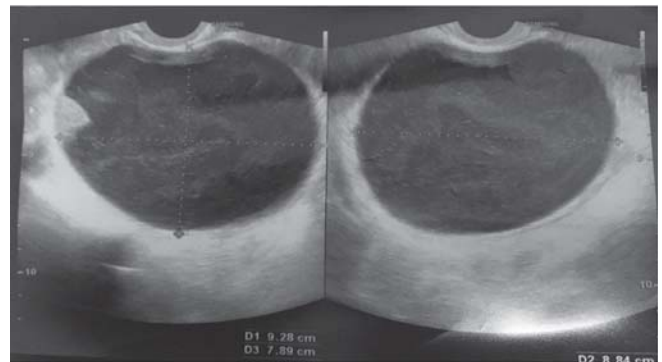
**Figure 4.** Index patient with grossly normal female external genitalia with sparse pubic hair.

Whole abdomen ultrasound showed visualization of bilateral kidneys with note of nephrolithiasis on the left, and pelvic mass probably ovarian in origin. Initial assessment was pelvic mass to consider Ovarian New Growth rule out malignancy versus Gonadoblastoma or Seminoma; Primary Amenorrhea secondary to Androgen Insensitivity Syndrome. She was subsequently referred to the Reproductive Endocrinology and Infertility service for co-management. Transvaginal ultrasound revealed

absent uterus and cervix and a pelvic unilocular, cystic structure measuring 10.27cm x 10.8cm x 10.27cm with low to medium level echoes within. The capsule measures 0.35 cm, color flow mapping revealed absence of vascular flow. Ultrasound impression was pelvic mass consider ovarian new growth probably benign by IOTA subgroup and Sassone Score 6 (Figure 5). Blood test results include the following: elevated FSH and LH levels (28.4 mIU/ml and 79.1 mIU/ml respectively), and testosterone of 9.2 nmol/L; serum LDH 200.22 U/L, Serum B-HCG of 3.96, CA-125 of 21.36 U/ml, AFP of 1.26 IU/ml. All tumor markers were within normal range. Karyotyping showed 46, XY (Figure 6). An abdominal CT scan (Figure 7) showed a 9.5cm x 9.2cm non-enhancing cystic lesion in the pelvis above the urinary bladder without enhancing solid component, that may represent a large Mullerian duct cyst that compresses the urinary bladder and may have caused urinary frequency.

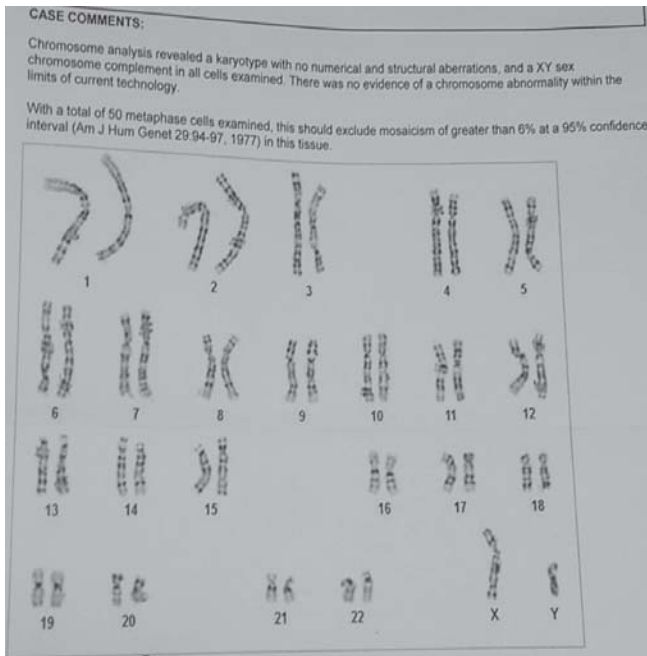
The plan for the patient was for laparoscopy with possible exploratory laparotomy and intraoperative referral to the urology service.

On laparoscopy, the mass was midline, with smooth white external surface, measuring 10cm x 10cm (Figure 8). The cyst had filmy adhesions to the bowels and pelvic sidewalls. On referral to urologist on board, the cyst was assessed to be possibly malignant. Hence, laparoscopy was converted to exploratory laparotomy. On laparotomy, urology service assessed the left cystic mass to be testicular in origin (Figure 9), and the right testis as atrophied (Figure 10). Both specimens were sent for histopathology.

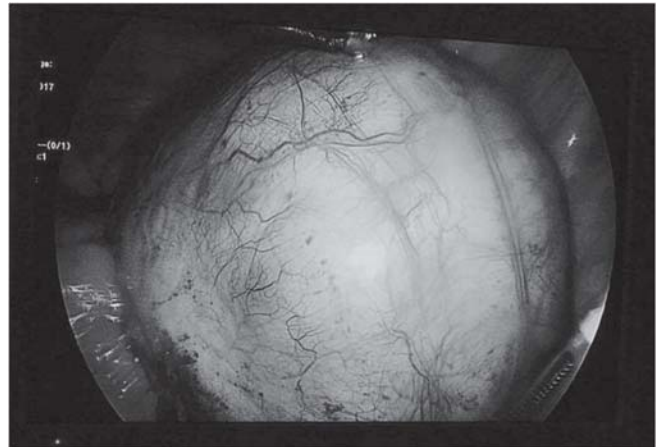


**Figure 5.** Transvaginal ultrasound showing pelvic mass with benign sonologic features.

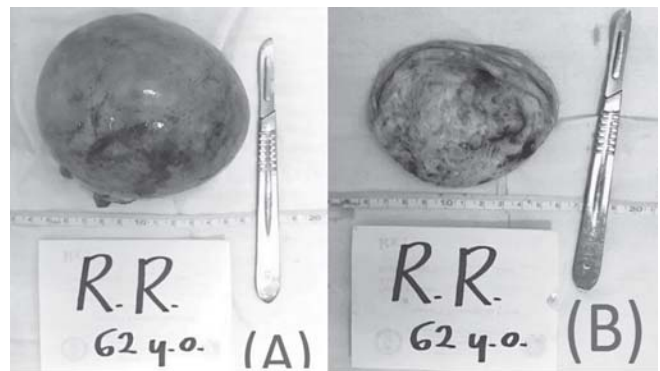




**Figure 6.** Karyotyping result showing 46 XY.



**Figure 8.** Laparoscopic view of pelvoabdominal mass.



**Figure 9.** (A) Pelvoabdominal mass, serous cyst (B) Pelvoabdominal mass on cut section.



**Figure 7.** Whole abdomen CT scan showing non enhancing mass in the pelvis with no solid lesions.

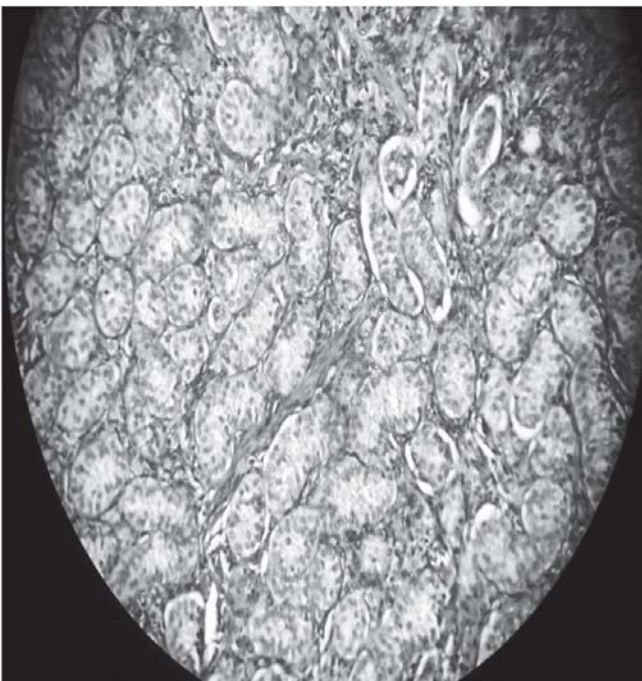


**Figure 10.** Right atrophied testis.

The patient tolerated the procedure well and was subsequently discharged on her third post-operative day. Histopathologic examinations revealed: (a) Pelvoabdominal mass identified as Serous Cyst (Figure 11); (b) Right testis, consistent with cryptorchid testis (Figure 12); (c) Cyst fluid: negative for malignant cells.



**Figure 11.** Pelvoabdominal mass, identified as serous cyst (Scanner view).



**Figure 12.** Histopathologic result: Right testis (LPO view).

## Discussion

Androgen Insensitivity Syndrome (AIS) is a condition wherein affected individuals have an XY chromosome and secrete normal levels of testosterone. However, there is lack of receptor activity in their targeted end organs resulting to deficient male internal and external genitalia. Individuals with CAIS present with phenotypically female external genitalia.<sup>3</sup> AIS is inherited in an X-linked recessive fashion, although 30% are de novo mutations.<sup>4</sup> The gene responsible for the AIS phenotype is found on the proximal, long-arm of the X-chromosome at Xq11-12.<sup>5</sup>

The development of male phenotype occurs when androgens exert its effects on androgen receptors (AR). In male embryos, the testes start to secrete androgens as early as 9 weeks of gestation. Testosterone peaks during 11 and 18 weeks gestation. This stimulates the Wolffian duct system into epididymis, seminal vesicle and vas deferens. A more potent, Dihydrotestosterone (DHT) stimulates development of male external genitalia including the penis and scrotum. Both hormones require activity of androgen receptors in their targeted tissues.<sup>6</sup> Anti-Mullerian hormones are secreted by Sertoli cells in fetal testes which functions in regression of Mullerian ducts. Without AMH production, there is development of the fallopian tube and uterus. In the case of AIS, Anti-Mullerian hormones are secreted normally. Hence, there is inhibition in the growth of the fallopian tubes and uterus, as what was seen in this patient.

The three classifications of AIS according to genital phenotype are as follows: complete (CAIS); partial (PAIS) and mild (MAIS) androgen insensitivity syndrome.<sup>7</sup> In the case of the index patient, she is diagnosed with CAIS since she has normal female external genitalia with absent or scant axillary and pubic hair.

In the Philippines, there have been six published cases of Androgen Insensitivity Syndrome (Ladines, 1982; Cruz, Morales and Bongala, 2000; Alday-Atienza, 2002; Ang-Sy, Tan-Garcia, Garcia, 2007; Lipana, Tanangonan, 2009; Villafuerte, Soriano-Estrella, 2016). All cases were diagnosed when the patients were in their second or third decades of life. One case presented with CAIS in

a 70-year old patient with inguinal testes.<sup>8</sup> This case presents the first patient diagnosed locally in an elderly with an intra-abdominal testes, with a benign pathology.

The most common presentation of CAIS is primary amenorrhea in a female adolescent, usually during the second decade of life. It can also present as inguinal hernia in an infant or child with an incidence rate of 1.1%.<sup>4</sup> The testes may be located as labial swelling or intra-abdominally. The first diagnosis of CAIS after the fifth decade of life is rare and that the risk of malignant transformation of the gonads increases with age. There is a 3% risk of malignancy at age 20, and this increases to 30% by age 50.<sup>9</sup> In the index patient, malignancy was considered because of the age and the location of the testes.

Having an intraabdominal testis in a patient with CAIS is quite rare in the literature. The most commonly seen tumor in dysgenetic gonads is Gonadoblastoma. Rutgers, et al. had reported malignant changes in their series of 43 patients with testicular feminization. Germ cell tumor remains the most common tumor in testicular feminization.<sup>10</sup> Sex-cord stromal tumor can also be presented as an intraabdominal testes with testicular feminization syndrome exhibited heterogeneity in both texture and contrast enhancement. Case reports in CAIS with intraabdominal testis typically present with malignant tumors.<sup>11</sup> Fortunately for the index patient, the histopathologic findings were benign.

The diagnosis of AIS is based on physical examination, history, karyotyping, endocrine

evaluation, imaging studies and histologic examination. Differential diagnosis would include Mullerian Agenesis or Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. Individuals with Mullerian agenesis have a 46, XX karyotype, which makes karyotyping integral in making a diagnosis (Table 1).<sup>4</sup>

Aside from the clinical findings of absent uterus, short blind-ending vagina, scant or absent pubic and/or axillary hair, individuals show a pattern consistent with an X-linked trait with reports of other family members exhibiting the same clinical findings. The 76-year old sibling of the index patient was not tested and examined but she also presented with primary amenorrhea. Pelvic ultrasound, CT scan or the gold standard MRI should be obtained to document the internal anatomy.<sup>4</sup> The endocrine profile shows: normal to high testosterone; normal to high FSH; mildly elevated LH due to negative androgen feedback.<sup>7</sup>

The management of patients with Androgen Insensitivity Syndrome requires a multidisciplinary approach. The Multidisciplinary team (MDT) is composed of a gynecologist, endocrinologist, urologist, psychologist and clinical geneticist. The duty of the medical practitioner is to act in the best interest of the patient and to treat the patient in a way that produces maximum benefit.<sup>12</sup>

The standard surgical management for CAIS is orchiectomy. This should be performed after puberty because of the risk of malignant transformation of up to 30%.<sup>4</sup> The patient has reached breast and height development. Sex identity is already established. Sexual identity and

**Table 1.** Difference between Mullerian agenesis and androgen insensitivity.

	Mullerian Agenesis	Androgen Insensitivity
Genotype	46, XX	46, XY
Heredity	Not known	Maternal X-linked recessive; 25 % risk of affected child, 25% risk of carrier
Sexual hair	Normal female	Absent to sparse
Testosterone level	Normal female	Normal to slightly elevated male
Other abnormalities	Frequent	Rare
Gonadal neoplasia	Normal incidence	5% incidence of malignant tumor



sexual rearing was not a problem in the case of the patient. At age of 62, she has a solid foundation of her femininity. She is married for 32 years, has adopted 2 children, and is already a grandmother.

Medical management for patients with AIS is composed of Hormonal Replacement Therapy (HRT) and psychological support. HRT is required for adolescent and adult AIS patients. Estrogen therapy is needed to initiate puberty, maintain feminization and to prevent osteoporosis.<sup>13</sup>

Plan for the patient is to do work up for osteoporosis on an out-patient basis and give appropriate management. Follow up with urology service was also advised.

Based on Beauchamp and Childress ethical principles, it is important to disclose the genotype of AIS at the time of diagnosis. If the diagnosis was made during infancy or soon after, together with a psychotherapist, the parents are responsible in making the decision when to disclose the diagnosis to the patient. If diagnosis was made during adolescence, the patient and her family are informed immediately.

In the case of the patient, she was informed of her diagnosis as soon as the karyotyping result was obtained. She exerted autonomy in her decision to give full disclosure about her condition to her husband. This knowledge of her condition did not seem to harm the relationship between her and her husband. Her spouse was very emotionally supportive and continued to be her caregiver all throughout her stay at this institution. Regardless of age at diagnosis, CAIS often cause psychological distress for the patient and her family. Long term counselling is strongly encouraged.

## Conclusion

This is a rare case of complete androgen insensitivity syndrome with intra-abdominal testes in a 62 year-old phenotypically female patient who presented with a pelvic mass, primary amenorrhea and a 46, XY karyotype. Surgical intervention revealed a benign cystic mass histopathologically, and intraabdominal testes. Patient was managed through a holistic multidisciplinary approach which includes not

only medical and surgical treatment of her condition, but also psychological counseling and support provided by an expert and her immediate family members.

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