Complete Androgen Insensitivity in Two Filipino Siblings: A Case Report

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Case Summary

Androgen insensitivity syndrome is an X-linked recessive condition resulting in a failure of normal masculinization of the external genitalia in a chromosomally male individual. We describe two phenotypically female siblings aged 27 and 18 years, who presented with primary amenorrhea. The older sibling first consulted because of her desire to be pregnant while her younger sibling consulted upon the physician's advice. Clinical presentation, physical examination, hormonal and imaging studies and a male (46XY) karyotype confirmed the diagnosis of Complete Androgen Insensitivity Syndrome (AIS) in both individuals. Both of them underwent exploratory laparotomy with histopathology confirming presence of immature testicular tissue. Hormone replacement therapy was then started. Both were advised to undergo psychosocial counseling and both chose to be women. This case report is significant since there are only a few local case reports about siblings presenting with this condition.

Keywords: Primary Amenorrhea, Androgen Insensitivity Syndrome, Karyotyping

Introduction

Androgen insensitivity syndrome (AIS) is an X-linked recessive condition resulting in a failure of normal masculinization of the external genitalia in chromosomally male individuals. It is caused by an X-linked mutation in the Androgen Receptor (AR) gene that expresses a variety of phenotypes ranging from male infertility to completely normal female external genitalia. The clinical phenotypes of AIS could vary and be classified into three categories, as complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS), according to the severity of androgen resistance.

Since we found no published data regarding siblings affected with Complete Androgen Insensitivity Syndrome (CAIS) here in the Philippines, this case report will describe the approach to diagnosis and the multidisciplinary management of siblings affected with this condition.

Case Presentation

Patient A: A 27-year-old Filipino female, naturally born to parents of non-consanguineous marriage was referred for evaluation of primary amenorrhea. Patient is the eldest among three children. Patient was born in a hospital setting with no perinatal complications noted. Childhood history was unremarkable, developmental milestones were at par for age.

Patient had no complaint until at the age of 12 when she noted an episode of vaginal spotting that lasted for one day. This was not associated with other symptoms such as hypogastric pain and was not associated with pelvic trauma, but with no menstruation thereafter. At 15 years old, she had her first evaluation with a gynecologist due to amenorrhea. At that time, evaluation showed delayed breast development (Tanner Stage 1) with no axillary hair and no pubic hair. The transrectal ultrasound showed absence of uterus and non-delineated ovaries. Patient was lost to follow up and no further work-up was done for 12 years. Patient noted the beginning of breast development when she was 17 years old. Interval history revealed that the patient underwent right inguinal herniorrhaphy at 18 years of age. At 20 years of age, full development of the breasts was achieved with sparse

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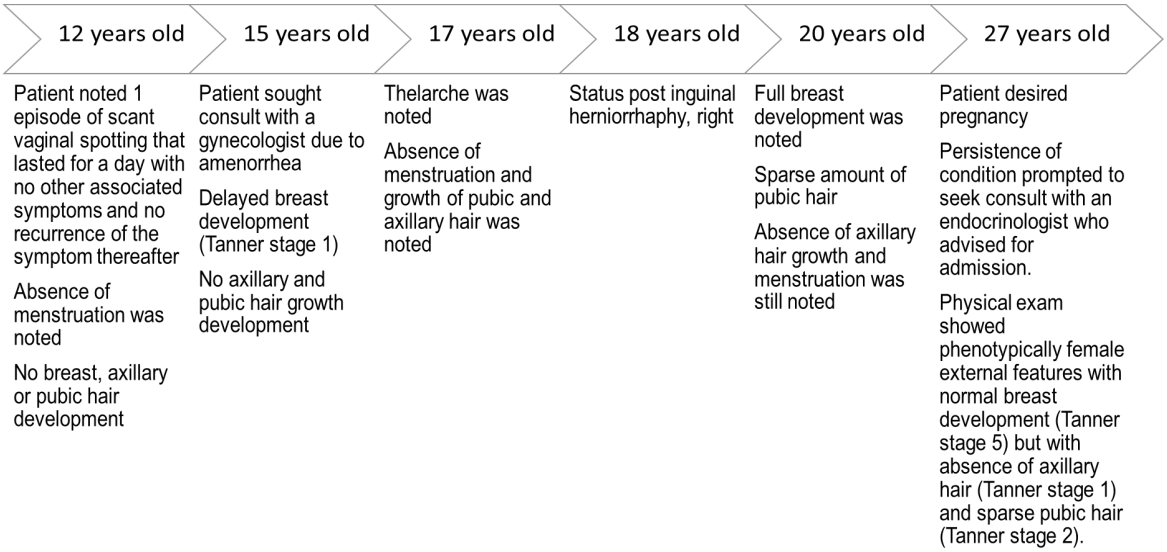
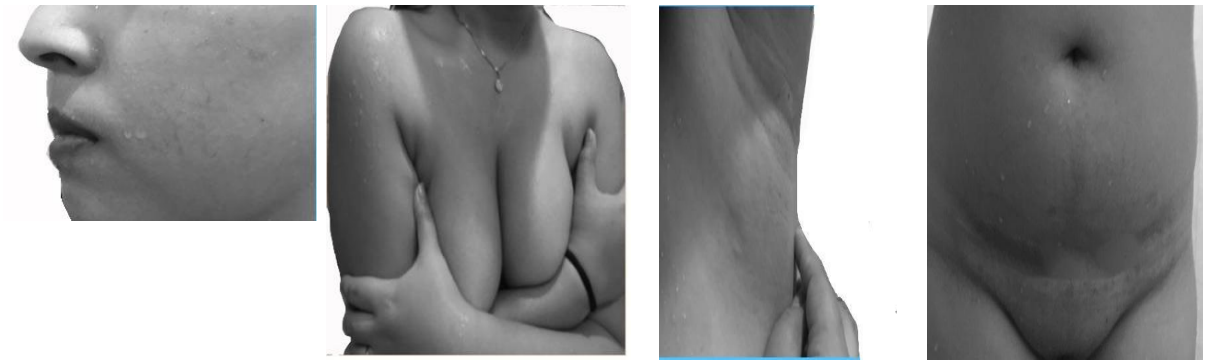


Figure 1. Diagram showing sequence of events for Patient A



A. Absence of facial hair and acne

B. Normal breast development (Tanner stage 5)

C. Absence of axillary hair (Tanner stage 1).

D. Sparse pubic hair (Tanner stage 2).

Figure 2. Pertinent Physical Examination Findings of Patient A

pubic hair growth. Absence of axillary hair growth and menstruation were still present noted.

At the current age of 27 years old, patient was already in a long-term relationship with a person of the opposite sex and desired pregnancy. Work-up with an endocrinologist was sought for the primary amenorrhea. The sequence of events for Patient A is depicted in *Figure 1*. On physical examination, she had phenotypically female external features with normal breast development (Tanner stage 5) but with absence of axillary hair (Tanner stage 1) and sparse pubic hair (Tanner stage 2) (See Figure 2). On pelvic examination, it revealed a grossly normal external female vagina, pinkish labia minora and majora, and absence of clitoromegaly. Internal examination revealed a blind-ending vagina, 6 cm in length.

A transrectal ultrasound was done which revealed intact vagina but with absence of uterus and cervix. The right gonad was intact while the left gonad was described as a cystic follicle. Confirmation with an abdominal magnetic resonance imaging (MRI) with contrast revealed a consistent result of a non-visualized uterus with a blind vaginal canal, a cystic lesion in the left pelvic sidewall measuring 1.7 x 1.7 x 2.3 cm and a mixed signal, heterogeneously enhancing soft tissue lesion noted anteromedial to the cystic lesion measuring approximately 3.2x2.0x3.5 cm (*Figure 3*). Karyotyping was done which revealed 46, XY male karyotype (*Figure 4*).

Patient B: The younger sibling of Patient A, is an 18-year-old Filipino, phenotypically female, also sought consult

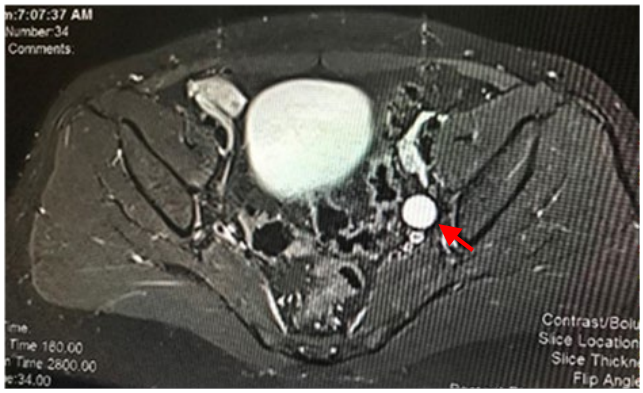


FIGURE 3. MRI of the whole abdomen with contrast of Patient A

The uterus is not visualized. A blinding pouch is noted in the distal end of the vaginal canal. There is no abnormal fluid accumulation within the pouch of Douglas.
There is a 1.7x1.7x2.3 cm non-enhancing cystic lesion in the left pelvic sidewall, as pointed by the red arrow. A mixed signal, heterogeneously enhancing soft tissue lesion is also noted anteromedial to the cystic lesion measuring approximately 3.2x2.0x3.5 cm.

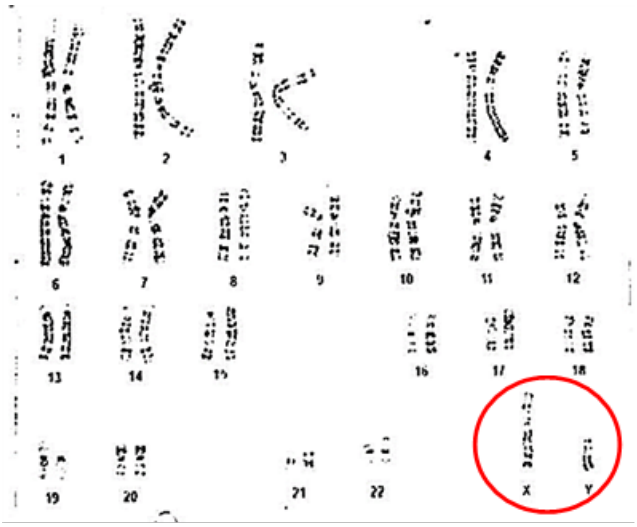


Figure 4. Karyotyping of Patient A. Patient is chromosomally male as evidenced by complete X and Y chromosomes

for evaluation of primary amenorrhea. Patient's childhood and medical history were unremarkable.

At 14 years old, the patient noticed no onset of menstruation. Also at this age, patient had no breast development and there was absence of pubic and axillary hair. At 15 years old, she was advised to undergo right inguinal herniorrhaphy, but at that time did not consent. Thelarche was noted at age 16 years old.

At the current age of 18 years old, patient B also decided to undergo work up along with her older sibling. The sequence of events for Patient B is shown in *Figure 5*. On physical examination the patient was noted to have well-developed breasts (Tanner Stage 5), sparse axillary hair (Tanner stage 2) and absent pubic hair (Tanner stage 1) (See *Figure 6*). Pelvic examination showed grossly female genitalia with no clitoromegaly. On bimanual examination, no uterus could be palpated.

Transrectal ultrasound showed hypoplastic/unicornuate uterus and non-delineated gonads. Further imaging by abdominal MRI with contrast confirmed the absence of a uterus that was probably hypoplastic (*Figure 7*). There is presence of a blind-ending vaginal canal and an enhancing soft tissue mass on the left side of the pelvis, measuring 2.9x2.0x3.4 cm which may represent a left

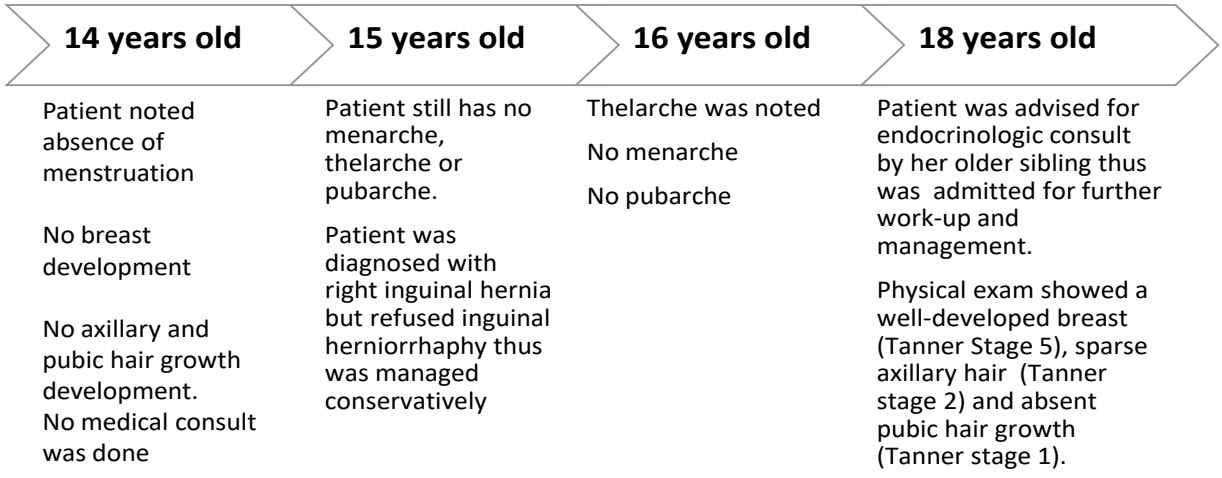
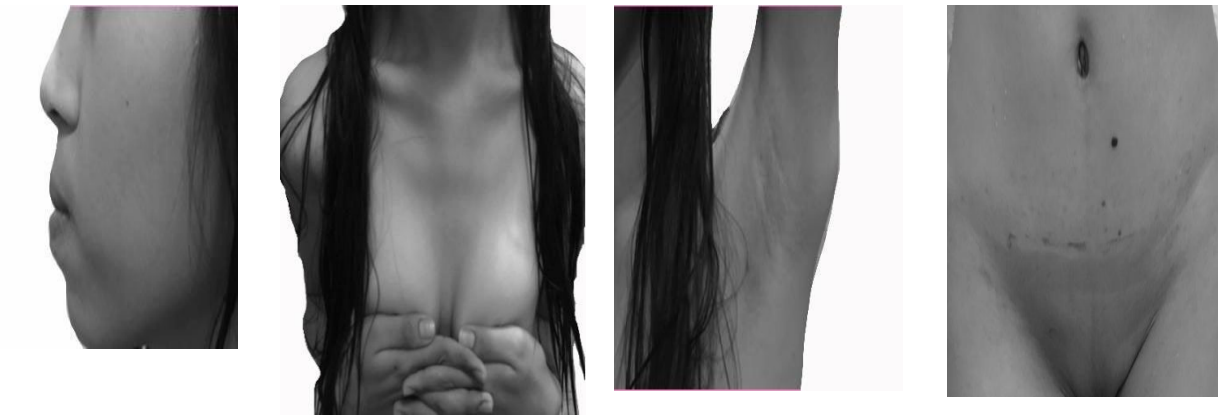


Figure 5. Diagram showing sequence of events for Patient B



A. Absence of facial hair and acne

B. Normal breast development (Tanner stage 5)

C. Sparse axillary hair (Tanner stage 2)

D. Absence of pubic hair (Tanner stage 1).

Figure 6. Pertinent Physical Examination Findings of Patient B

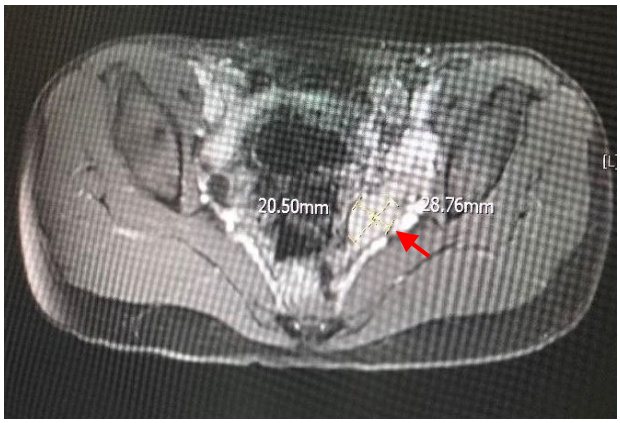


Figure 7. MRI of the whole abdomen with contrast of Patient B

The uterus is not identified. There is a tubular structure between the rectum and urinary bladder which may represent a vaginal canal. There is an enhancing soft tissue mass in the left side of the pelvis, measuring 29x20x34 mm which may represent a left ovary, as pointed by the red arrow.

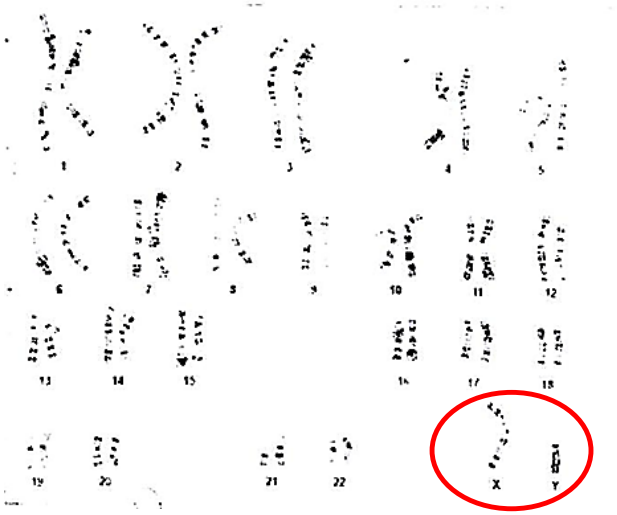


Figure 8. Karyotyping of Patient B. Patient is chromosomally male as evidenced by complete X and Y chromosomes

ovary. Ultimately, karyotyping was done which revealed 46, XY karyotype (*Figure 8*).

A family genogram was made showing patient A, aged 27 years old and patient B, aged 18 years old, both presenting with primary amenorrhea. A red dot in the genogram signifies the possible carrier state of the mother for CAIS (*Figure 9*).

Hormonal profile of both patients showed normal results except for the unusual elevation of Luteinizing Hormone (LH) levels and androgen level (Testosterone/Free testosterone) (*Table I*).

A family conference was held to discuss the condition of both patients and the risk of having future gonadal malignant transformation if operation of the gonads was not to be done. Both patients underwent pelvic exploration with bilateral gonadectomy. Intraoperative findings for patient A showed a right testicle with adherent bowel and a 1x1 cm cystic pedunculated mass, a hypoplastic uterus 2x1 cm adherent to the proximal portion of the right testicle and a left testicle and epididymis located anterior to the appendix. Final histopathology of patient A revealed an immature testicular tissue on both right and left adnexal mass, a benign mesothelial cyst and a muscular tissue grossly compatible with small uterine tissue (*Figure 9*). On the other hand, intraoperative findings of patient B showed 3 x 2 cm left mass attached pelvic wall and a 3 x 2 cm ovoid mass with 4 x 5 cm elongated firm mass on the right pelvic wall with attachment to the hypogastric area. Final

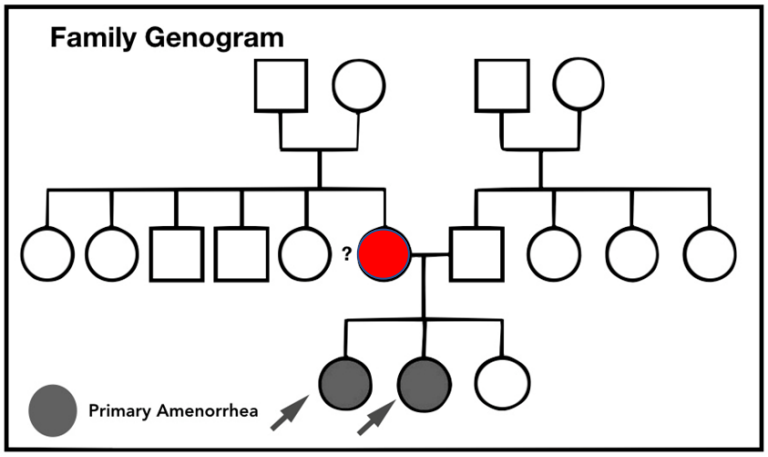


Figure 9. Family Genogram. This family genogram shows Patient A and Patient B, pointed by the arrows, diagnosed with Complete Androgen Insensitivity Syndrome. The red circle signifies the possible carrier state of the mother for CAIS.

Table I. Hormonal Profile of Both Patients

Tests	Reference Ranges	Patient A	Patient B
Follicle Stimulating Hormone (FSH)	1.5-12.5 mIU/mL	8.23 mIU/mL	1.3 mIU/ml
Luteinizing Hormone (LH)	1.7-8.6 mIU/mL	20.38 mIU/mL	32.3 mIU/ml
Estradiol	Female 12.5-166 pg/mL Male 1.7-58.6 pg/mL	28.30 pg/mL	27.64 pg/mL
Dehydroepiandrosterone sulfate (DHEA-SO4)	95.8-511.7 ug/dL	502.90 ug/dL	306.80 ug/dL
Free testosterone	0.3-1.9 ng/dL	8.4 ng/dL	12.22 ng/ml
Serum Creatinine	0.6-1.5 mg/dl	0.69 mg/dl	0.8 mg/dl
SGPT	5.0-50.0 U/L	64.0 U/L	17 U/L
Serum Sodium	134-148 mmol/L	138 mmol/L	138 mmol/L
Serum Potassium	3.3-5.3 mmol/L	3.5 mmol/L	3.5 mmol/L
Thyroid Stimulating Hormone (TSH)	0.30-5.0 uIU/mL	1.49 uIU/mL	
FT4	Female: 11.0-22.5 pmol/L	13.95 pmol/L	16.86 pmol/L
Prolactin	102-496 mIU/L	111.8 mIU/L	104.1 mIU/L

histopathology report revealed immature testicular tissue with benign mesothelial cysts on both masses (*Figure 10*).

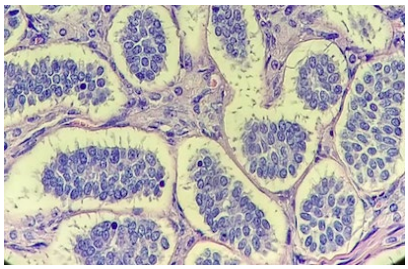
Their surgeries went well. There were no complications seen on both patients peri- and post-operatively and during the succeeding post-operative recovery days.

For hormonal replacement therapy, patient A was started with transdermal estrogen gel (Estradiol 600 mcg/g) 2.5grams applied once a day. Choice of route for estrogen was based on the slightly elevated liver enzymes due to non-alcoholic fatty liver disease. A gastroenterologist assessed Patient A to have non-alcoholic fatty liver disease (NAFLD). Patient A was advised to lose weight through exercise and medical nutrition therapy. The plan was to eventually shift transdermal estrogen gel to oral estrogen once liver enzymes improved to acceptable levels. For patient B, the patient was started with Tibolone 2.5 mg 1 tablet once a day.

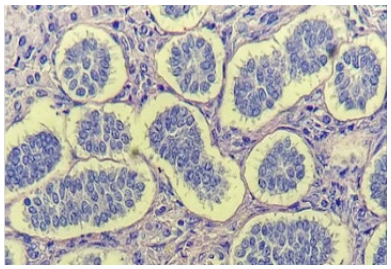
Calcium with Vitamin D oral supplements were started and both patients were advised to have baseline bone mineral densitometry (BMD)/Dual-energy X-ray Absorptiometry (DEXA) to be followed up after a year post-gonadectomy for surveillance and prevention of osteoporosis. There were no adverse reactions to therapeutic interventions on both patients. Both patients showed good compliance to medications.

Both patients were referred to a psychologist. Patient A was seen and evaluated by a psychologist and assessed to have normal mental status examination without signs of mental disorder and depression. Her overall psychological response was within normal. Unfortunately, patient B failed to meet with the psychologist for her appointment due to busy school schedule thus was advised to for follow up.

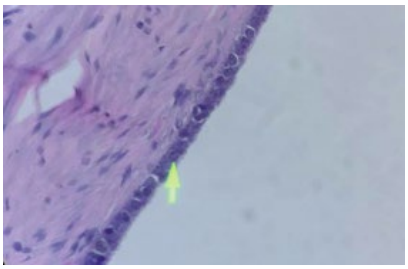
Genetic counseling with a geneticist and psychological counseling were advised. The mother and the third sibling were also advised for genetic work-up because of



Left Gonad

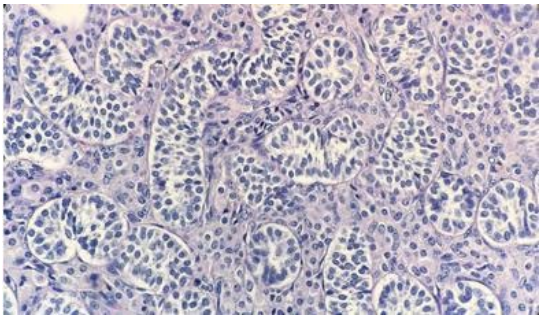


Right Gonad

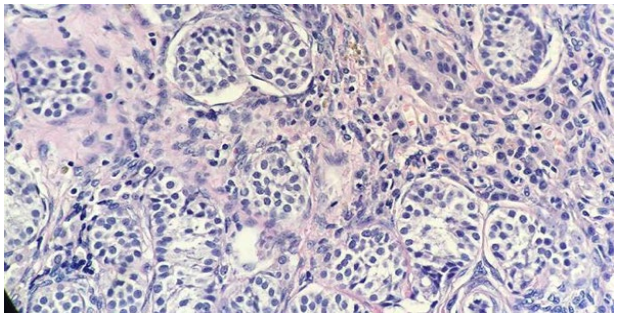


Right Benign Cyst

Figures 9. Final histopathology report of Patient A revealed immature testicular tissue on both right and left adnexal mass, benign mesothelial cyst and a muscular tissue grossly compatible with small uterine tissue.



Left Gonad



Right Gonad

Figure 10. Final histopathology report of Case B revealed immature testicular tissue with benign mesothelial cysts on both intraabdominal masses submitted.

the possibility that they might be carriers of Androgen Insensitivity Syndrome but no testing was done yet.

Case Discussion

AIS is typically characterized by evidence of feminization of the external genitalia at birth, abnormal secondary sexual development in puberty and infertility in individuals with a 46, XY karyotype.[1] This condition was described for the first time in 1953 by John Morris, who studied the clinical features of 82 patients and previously termed AIS as testicular feminization syndrome.

AIS represents a range of defects in androgen action and can be subdivided into three phenotypes: complete androgen insensitivity syndrome (CAIS) with typical female external genitalia, partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male or ambiguous external genitalia and mild androgen insensitivity syndrome (MAIS) with typical male external genitalia. Complete androgen insensitivity syndrome is the most frequent cause of development sexual disorder (DSD) with estimated frequency of 1:50,000 and 100,000 male births.[2] In the Philippines, there are a total of 14 published cases of CAIS in the Philippine Journal of Reproductive Endocrine and Infertility and Philippine Journal of Obstetrics and Gynecology. But there has been only one case report published in 2002, demonstrating the rarity of this condition among Filipino siblings.[3,4]

Mutations in the AR gene cause androgen insensitivity syndrome. The AR gene is a single copy gene that spans ~90 Kb of genomic DNA and lies on the X-chromosome at Xq11–12, responsible for the synthesis of androgen receptors.[5] These receptors allow cells to respond to androgens, such as testosterone and dihydrotestosterone to direct male sexual development. Mutations in the AR gene, such as complete or partial deletions, point mutations or small insertions, prevent androgen receptors from working properly, which makes cells resistant to androgen stimulation. Depending on the level of androgen insensitivity, an affected person's sex characteristics can vary from mostly female to mostly male.[6] About 70% of AR mutations are inherited and transmitted in an X-linked manner, while the rest are sporadic mutations.[7]

There are three scenarios in which CAIS is diagnosed: in fetal life when prenatal sex determination disclosed a 46, XY karyotype in a fetus with female external genitalia; inguinal masses in an otherwise healthy female child and at puberty in females with primary amenorrhea. The presence of inguinal hernia in a female child is rare and could indicate a CAIS diagnosis.[8] In both of our patients, they presented with inguinal hernia and absence of menarche in their early teens which prompted work up for AIS.

In an adult patient with CAIS, breasts development is delayed with estradiol levels in normal male range,

suggesting the lack of androgen action.[7] This is the main driver of breast development in these patients, rather than an increased estrogen secretion. Due to insensitivity to androgen action, individuals with CAIS have normal female external genitalia with shortened blind-ending vagina with vaginal measurement varied from 2.5 to 8 cm. They also present with sparse or absent pubic and axillary hair.[2] These clinical features are all consistent in both of the patients presented.

To confirm the absence of pelvic structures, a trans-abdominal ultrasound is the first line of investigation to detect agenesis of Mullerian structure and to locate the presence and position of the testis.[9] However, ultrasound has an inferior capability of identifying pelvic structures therefore a pelvic magnetic resonance imaging (MRI) with contrast is requested. Magnetic resonance imaging (MRI) is the gold standard for imaging of the Mullerian structures, finding Wolffian remnants, evaluation of blind ending vagina, and abdominal and pelvic localization of testes as well as development of any gonadal malignancy.[10] Other differential diagnoses that were considered in both patients who presented with primary amenorrhea with breast development with presence of uterus include outflow tract disorder and other endocrinopathies such as prolactinoma, thyroid dysfunction and conditions associated with high testosterone levels. On the contrary, three differential diagnoses were considered in both patients with well-developed breasts but absent uterus, namely, CAIS, Congenital Absence of Uterus, or Mayer–Rokitansky–Küster–Hauser syndrome (MRKH), as shown in *Table II*.

The confirmation for the absence of Mullerian structures in a female patient with well-developed breasts, presenting with primary amenorrhea narrows the differential diagnosis to either CAIS or Congenital Absence of Uterus or Mayer–Rokitansky–Küster–Hauser syndrome (MRKH). In both our patients, both pelvic ultrasound and MRI confirmed the absent or hypoplastic uterus.

Women with complete androgen insensitivity syndrome who have intact gonads have the endocrine profile of a hormone-resistant state. Serum testosterone concentrations are either within or above the normal range for men or boys and luteinizing hormone (LH) concentrations are inappropriately increased.[8] This explains the unusual increased levels of testosterone and LH in both patients described. Karyotyping is done to arrive on the definite genotypic sex of an individual [11]. This distinguishes CAIS from MRKH pre-operatively. Individuals with MRKH can be distinguished from those with CAIS by confirmation of a 46,XX karyotype. The results of the karyotyping of both patients showed 46,XY which establishes the diagnosis of CAIS.

Management of androgen insensitivity syndrome is dependent on a multidisciplinary team and should address functional, sexual, and psychological issues such as disclosure, gonadectomy and subsequent hormone replacement, creation of a functional vagina, provision of genetic advice, coping strategies and long term follow up. Disclosure must be done carefully addressing issues like implications of an XY karyotype, presence of testis, absent uterus, sexual function, starting with parents initially with age-appropriate disclosure to patients.[12] Both patients underwent a complete evaluation by specialists in disorders of sex development to establish the extent of the disease and the needs of an individual diagnosed with CAIS. The family of both patients were advised for genetic testing but no testing was done by both parents and the third younger sister thus the limitation of this case study.

Table II: Differential Diagnoses for Primary Amenorrhea

Primary Amenorrhea with breast development with presence of uterus	Primary Amenorrhea with breast development but absent uterus
Outflow tract disorder Other endocrinopathies such as prolactinoma, thyroid dysfunction, and conditions associated with high testosterone levels	Complete androgen insensitivity syndrome Congenital Absence of Uterus Mayer–Rokitansky–Küster–Hauser syndrome (MRKH)

In CAIS, the risk of gonadal germ cell tumors (GCTs) is considered low and related to age. However, the risk of gonadal tumor development in CAIS increases with age. The combined malignant and premalignant gonadal histology prevalence is 6.0%.[13] As patients enter adulthood, the incidence rates have been reported to be 0.8% to 22% to those who have retained their gonads. The risk of malignancy for undescended intra-abdominal testes is 3.6% at 25 years-old, and 33% at 50 years-old.[14] The higher malignant transformation in older patients not having gonadectomy paved the way to the basis for the optimum timing for surgery.

It is recommended that prophylactic gonadectomy is optimally done at age 16-18 years old. This will allow achievement of final height and breast development and at the same time the risk of malignancy is manageable.[15] Results of the study of Chaudry et al, also support the current recommendation that gonads in CAIS can be retained until early adulthood.

Hormone replacement therapy (HRT) is started post-gonadectomy to maintain secondary female sexual characteristics, prevent osteoporosis and decrease cardiovascular morbidities.[16] Synthetic estrogens can be given in the form of the combined oral contraceptive pill but since women with CAIS do not have a uterus, they can be treated with continuous, unopposed estrogen. Starting HRT at the time of gonadectomy and continuing until at least the age of natural menopause (age 51-52) significantly reduces most, but not all, of the increased risks seen in untreated women.[16]

Several preparations are available which can be either given orally or trans-dermally. The choice is based individually to ensure compliance. In some studies, post-gonadectomy patients take testosterone because of the perceived benefit of testosterone in improving sense of

well-being (including libido).[17] These effects might be estrogen mediated from aromatization of testosterone. In the Philippine setting, widely available options are using oral estradiol, transdermal estradiol and the selective tissue estrogenic activity regulator (STEAR).[18] In patient A, she was started with transdermal estrogen gel since this avoids the first-pass effect of the liver, given that she has slightly elevated liver enzymes. On the other hand, patient B was given Tibolone 2.5 mg, 1 tablet once a day.

Additional treatment for CAIS may include vaginal dilatation to avoid dyspareunia. For prevention of secondary manifestations, regular weight-bearing exercises, supplemental calcium and vitamin D are recommended to augment bone health. Bisphosphonate therapy may be indicated for those with evidence of diminished bone mineral density and/or multiple fractures.[1]

Annual medical follow-up and surveillance checkup is necessary. This includes 1) Annual complete history and physical examination including breast examination, 2) Bone densitometry/DEXA scan every 1 to 2 years, 3) FBS, lipid profile, liver & renal function tests and annual mammogram.[20]

Psychosocial support is central to the multidisciplinary approach to management of complete androgen insensitivity syndrome.[21] Adolescents and parents of children with the disorder will have to make significant decisions at diagnosis about treatments and the timing and extent of any surgical interventions. Concerns should focus on assimilation of the disconnection between chromosomal, gonadal, and phenotypic sex and its implications. One legal aspect of importance is gender determination. There were no documented cases of self-reassignment gender determination in AIS case.[22]

In Philippine laws, the most important legal factor is the sex given by the birth attendant. Article 408 of the Civil Code clearly stated the sex of the newborn child as a requirement for registration of birth. Under these circumstances, the entry to the civil registry on the sex of the newborn of AIS is a flaw as it cannot determine with certainty the gender of the newborn. Once a scientific determination is completed, a petition to the court may be made to correct the entry in the birth certificate of the AIS patient**.** In this case, both of them chose to continue their roles as women in their daily lives.

Conclusion

This is a rare case report of Filipino siblings affected with Androgen Insensitivity Syndrome. Both patients were phenotypically females presenting with primary amenorrhea. Metabolic and hormonal investigations as well as imaging modalities and genetic testing were done to arrive at a diagnosis for this case. Prophylactic gonadectomy after completion of puberty negates the risk of malignant transformation in the future and at the same time allows proper development of final height and secondary sexual characteristics. Hormone replacement therapy is started post operatively to maintain female secondary sexual characteristics and prevent risk of osteoporosis and cardiovascular morbidity. Moreover, psychosocial counseling and sound legal advice completes the multidisciplinary approach in the management of these patients.

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