Androgen insensitivity syndrome (AIS)*

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ABSTRACT

Androgen Insensitivity Syndrome (AIS) is a rare condition, it is an X-linked-mutation that is considered as a disease caused by resistance of androgen receptor to its actions. It is expressed in a variety of phenotypes ranging from male infertility to completely normal female external genitalia. This is a case of a 25 year-old with Complete Androgen Insensitivity Syndrome (CAIS), presented as phenotypical female with secondary sexual development, bilateral inguinal masses. Gonadectomy, estrogen replacement therapy and psychological support are part of long term management.

Keywords: Androgen insensitivity syndrome, complete androgen insensitivity syndrome

INTRODUCTION

Man and woman are created to be a couple to fulfill each other's destinies. People say that the essence of being a woman is to become a mother, but what if a woman suddenly realizes she cannot be one?

Androgen Insensitivity Syndrome (AIS) is a rare condition where one is born with 46 XY chromosome, phenotypical female. AIS is a disease caused by resistance of androgen receptor to its action, causing the inability of the cells to respond to androgen both in the morphogenesis and differentiation of the body structures. It is a rare condition occurring in 1 in every 20,400 liveborn males.[1]

Androgen Insensitivity Syndrome is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). This means that Androgen Insensitivity Syndrome, or a subtype of Androgen Insensitivity Syndrome, affects less than 200,000 people in the US population. Ophanet, who are a consortium of European partners, currently defines a condition rare when it affects 1 person per 2,000. They list Androgen Insensitivity Syndrome as a "rare disease".[2]

Locally, the incidence of AIS is unknown. However there have been 4 cases reported in the Philippine Obstetrical and Gynecological Society in the past 5 years (Sandoval JF,2010; Soriano RC,2010; Fuentes AT,2011; Veranga CA,2012)

In this institution, this is the second case of AIS with the first reported on 2012 (Veranga CA,2012).

CASE REPORT

This is a case of R.P., a 25 years-old, nulligravid, single, from Mindoro consulted due to primary amenorhea.

Patient noted breast budding at 13 years-old, full breast development was noted at 18 years-old. She has no menses at this time.

Scanty pubic hair growth was noted at 16 years-old. It never transformed into the characteristic adult hair and she still has no menses at this time. At the same year she noted a moveable, reducible, non-tender, left inguinal mass measuring 2 x 1cm with no associated symptoms. Due to absence of menses, patient consulted an obstetrician-gynecologist and was advised ultrasound. Ultrasound was not done due to financial constraints.

At 20 years-old, her left inguinal mass was noted to increase in size to 2cm x 2cm thus patient consulted a surgeon and was diagnosed with hernia and advised surgery. She was also referred to an obstetrician-gynecologist due to amenorrhea and ultrasound was requested. Patient did not comply for surgery and ultrasound due to financial constraints. At this time patient's weight was noted to be 51 kg with height of 165cm.

At 21 years-old, another similar mass was noted at the right inguinal area measuring approximately 2 x 2 cm, moveable and non-tender. She still has no menses at this time. Patient did not seek consult to any physician due to financial constraints. She however noted a 4 kg weight loss in 1 year, from 51 kg to 47 kg.

At 22 years-old, patient started to have sexual activity with 1 sexual partner. Patient claims to have no difficulties in sexual contact. At this time patient's weight was 47 kg.

Patient tolerated the presence of bilateral inguinal masses, weight loss and amenorrhea due to financial constraints until she reached 25 years-old.

At 25 years-old, her weight was 43 kg, patient sought consult with a surgeon due to bilateral inguinal masses, amenorrhea and weight loss. The surgeon requested for both inguinal and pelvic ultrasounds. Inguinal ultrasound showed an ovoid hypoechoic nodule in the right region measuring about 2.76 x 2. 38 x 1.18 cm and small nodules

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in the left inguinal region measuring about 0.8 x 0.94 cm x 0.26 cm. Pelvic ultrasound confirmed a prepubertal uterus measuring only 2.8 x 1.77 x 2.09 cm. There were also small nodules seen at the adnexal area measuring about 2.03 x 1.41 cm on the right and 2.25 x 1.45 cm on the left which may represent small ovaries. Chest x-ray was normal at this time. Patient was referred to our institution due to primary amenorrhea and bilateral inguinal masses with associated weight loss.

Past medical history was unremarkable.

There were no heredofamilial disease noted such as hypertension, diabetes, asthma, cancer, thyroid and kidney diseases. Patient is the 3rd in a brood of 7. Patient claims her eldest sister has 4 children, her eldest brother has 2 children and the other younger sisters have regular menstrual cycles.

Patient is a non-smoker and non-alcoholic beverage drinker. She is currently unemployed.

In our institution patient was referred to the Reproductive, Endocrinology and Infertility (REI) section where on physical examination, patient was conscious, coherent, not in cardio respiratory distress with normal vital signs. There was no anterior neck mass noted. Patient has grossly normal breasts at Tanner stage V which showed recession of areola to the contour of the breast (Figure 1), flat abdomen (Figure 1), and no axillary hair (Figure 2). There were 2 palpable inguinal masses, measuring 4 x 3.5 cm on the right and 5 x 3 cm on the left, both of which were moveable, non-tender with the left inguinal mass reducible (Figure 3).

On pelvic examination, pubic hair was at Tanner Stage II with sparse, long, pigmented hair, primarily on the labia majora. Labia majora and labia minora were similar to prepubertal females with normal looking clitoris which measures 3 x 1.5 cm (Figure 4).

Speculum examination showed pinkish vaginal mucosa. The vagina seems to be a blind pouch and no cervix was appreciated (Figure 5). On internal examination, the vagina admits 2 fingers, with the length of the vaginal canal measuring 7 cm, no palpable cervix, no uterus and no adnexae appreciated. Retrovaginal examination was confirmatory with internal examination findings.

The initial consideration upon first consult in our institution was Primary amenorrhea (Figure 6) secondary to congenital absence of the uterus probably Androgen Insensitivity Syndrome versus Mayer Rokitansky Kuster

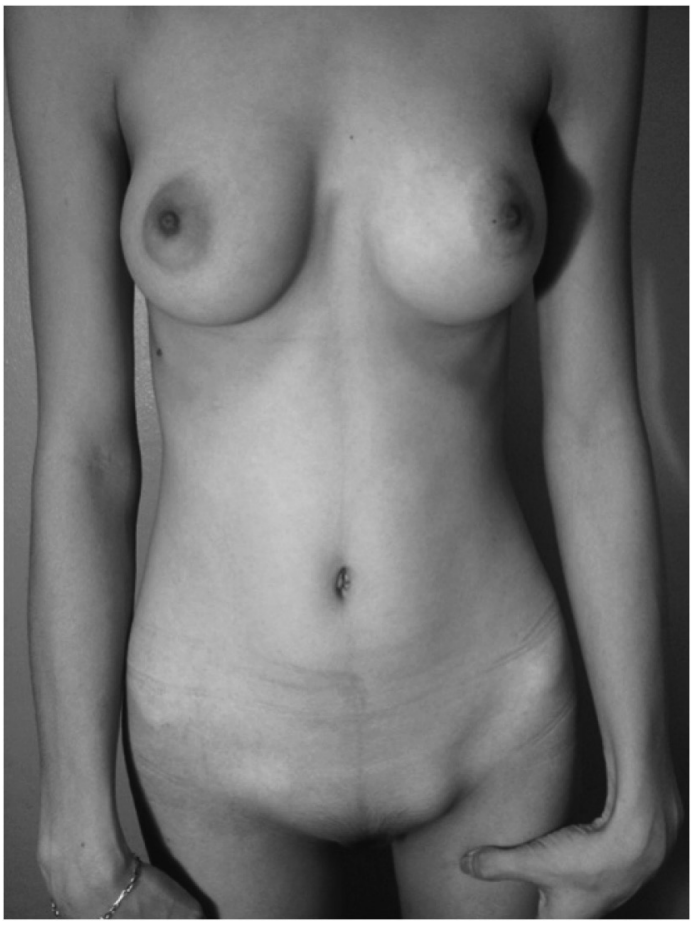


Figure 1. A normal looking breast with Tanner Stage V and flat abdomen

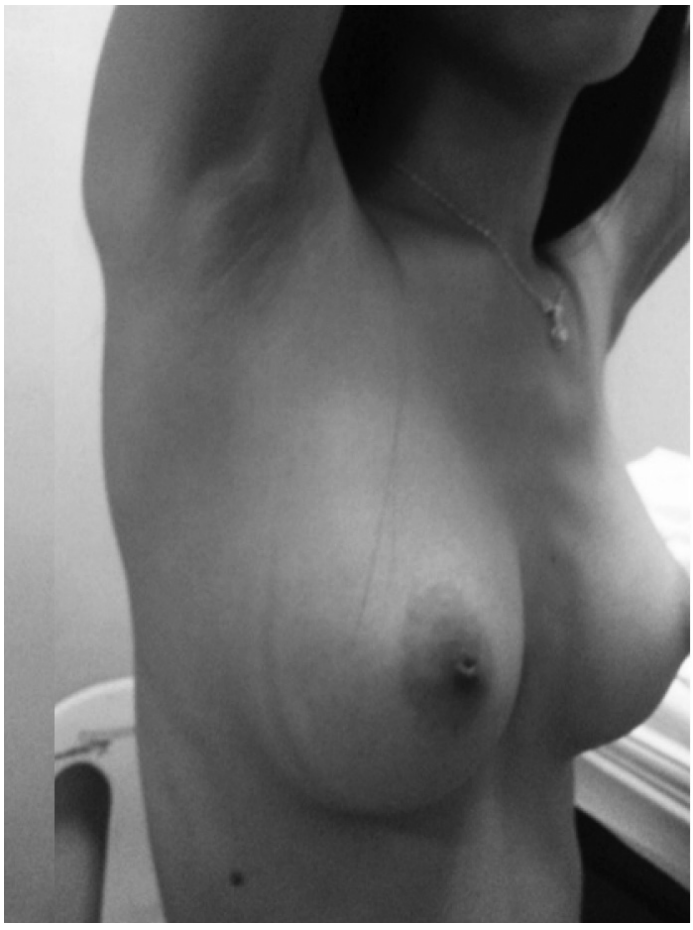


Figure 2. An axillary area showed absence of hair growth

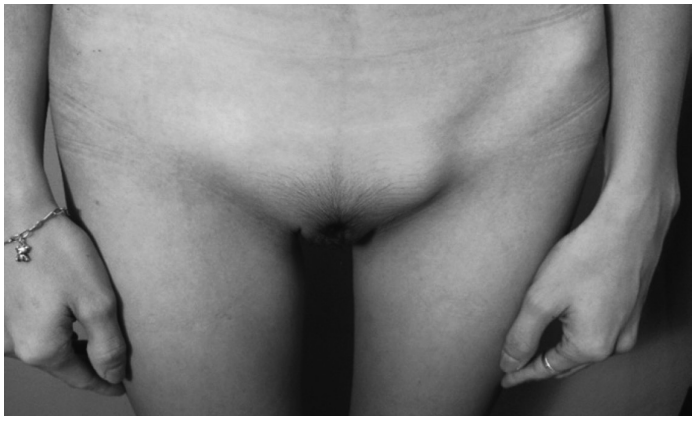


Figure 3. External Genitalia with scanty pubic hair Tanner Stage II, There is a bilateral mass on right inguinal area and left inguinal area

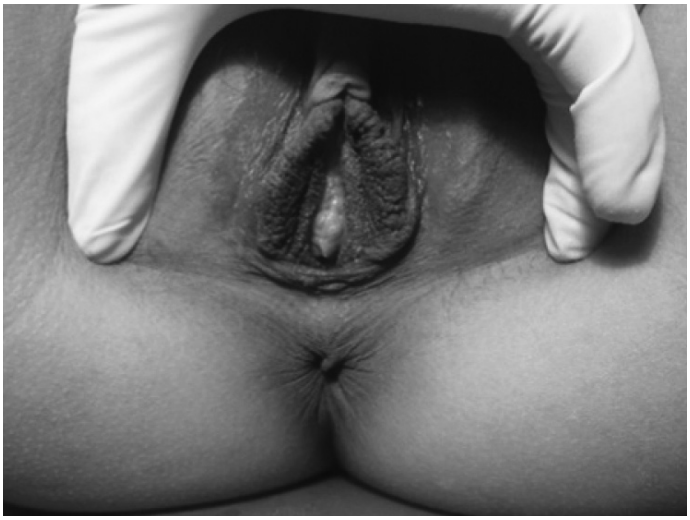


Figure 4. External Genitalia Examination: a normal looking of Labia Majora, Labia Minora and Clitoris

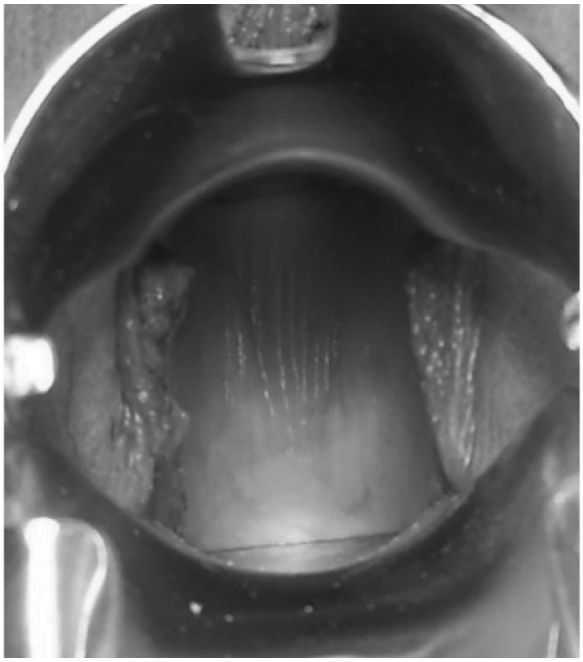


Figure 5. A blind pouch vagina with no cervix appreciated

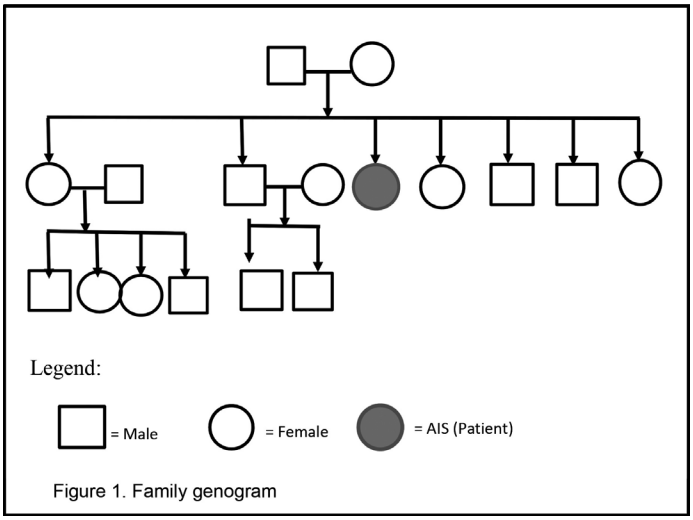
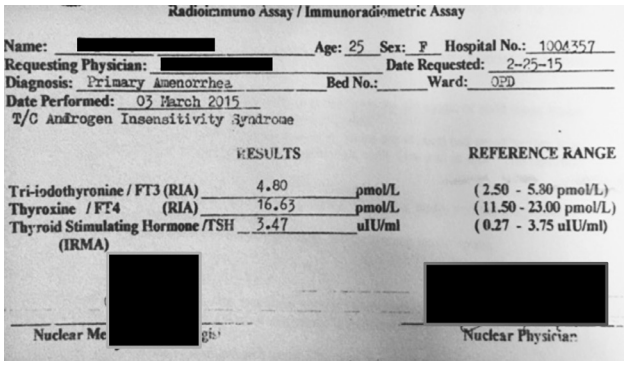


Figure 6. Algorithm in Diagnosing Primary Amenorrhea[23]

Hauser Syndrome, to consider left inguinal mass.

Pertinent laboratory examinations requested were Thyroid function test, Testosterone level and Chromosomal analysis. Thyroid function test were normal (Figure 7). The serum testosteroneis > 52.05 nmol/L (Figure 8), which is considered high for females (Ref 0.290-1.67 nmol/L) and high for male values (8.64-29.00 nmol/L). Chromosomal analysis revealed a 46 XY karyotype (Figure 9).

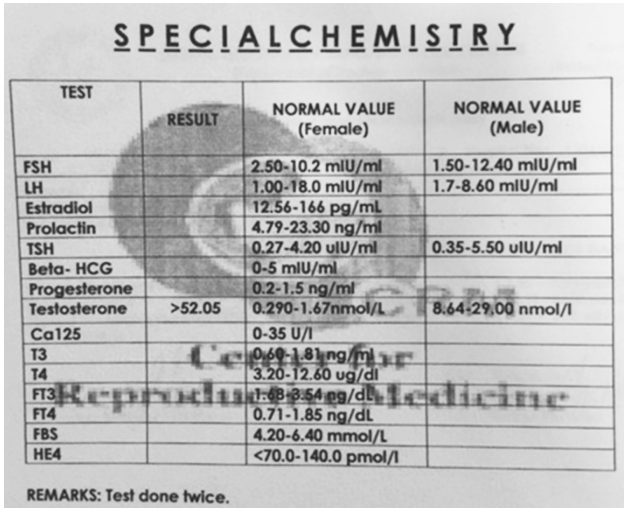

Radioimmuno Assay / Immunoradiometric Assay

Name: [redacted] Age: 25 Sex: F Hospital No.: 1004357
Requesting Physician: [redacted] Date Requested: 2-25-15
Diagnosis: Primary Amenorrhea Bed No.: Ward: OPD
Date Performed: 03 March 2015
T/C Androgen Insensitivity Syndrome

	RESULTS		REFERENCE RANGE
Tri-iodothyronine / FT3 (RIA)	4.80	pmol/L	(2.50 - 5.80 pmol/L)
Thyroxine / FT4 (RIA)	16.63	pmol/L	(11.50 - 23.00 pmol/L)
Thyroid Stimulating Hormone /TSH (IRMA)	3.47	uIU/ml	(0.27 - 3.75 uIU/ml)

[redacted] Nuclear Physician

Figure 7. Thyroid Function Test Result (February 25, 2015)


SPECIAL CHEMISTRY

TEST	RESULT	NORMAL VALUE (Female)	NORMAL VALUE (Male)
FSH		2.50-10.2 mIU/ml	1.50-12.40 mIU/ml
LH		1.00-18.0 mIU/ml	1.7-8.60 mIU/ml
Estradiol		12.56-166 pg/mL	
Prolactin		4.79-23.30 ng/ml	
TSH		0.27-4.20 uIU/ml	0.35-5.50 uIU/ml
Beta- HCG		0-5 mIU/ml	
Progesterone		0.2-1.5 ng/ml	
Testosterone	>52.05	0.290-1.67nmol/L	8.64-29.00 nmol/l
Ca125		0-35 U/l	
T3		0.60-1.81 ng/ml	
T4		3.20-12.60 ug/dl	
FT3		1.68-3.54 pg/dL	
FT4		0.71-1.85 ng/dL	
FBS		4.20-6.40 mmol/L	
HE4		<70.0-140.0 pmol/l	

REMARKS: Test done twice.

Figure 8. Testosteron Test Result (February 25, 2015)

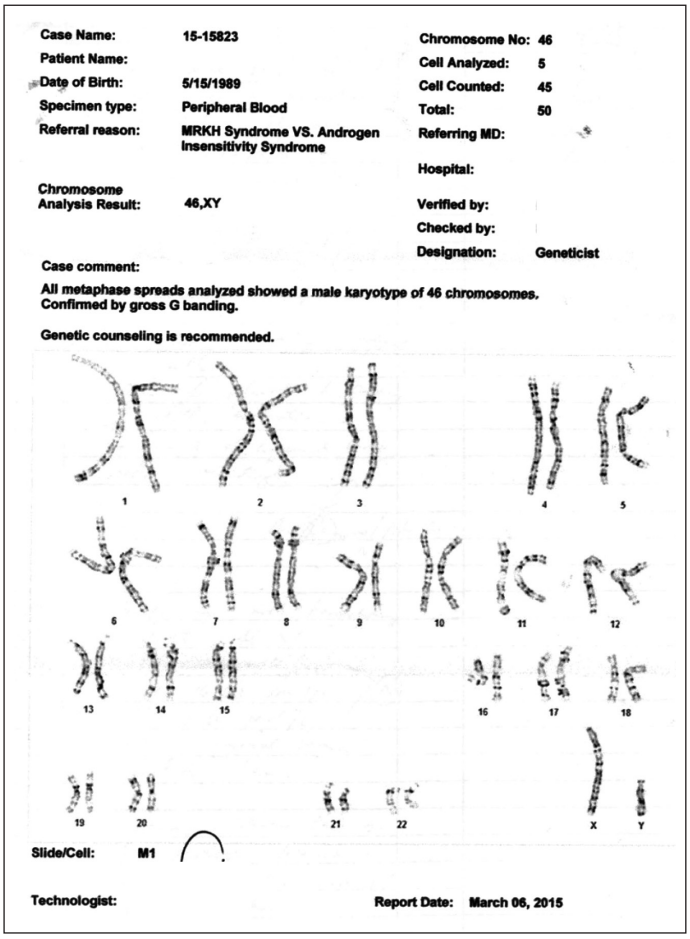
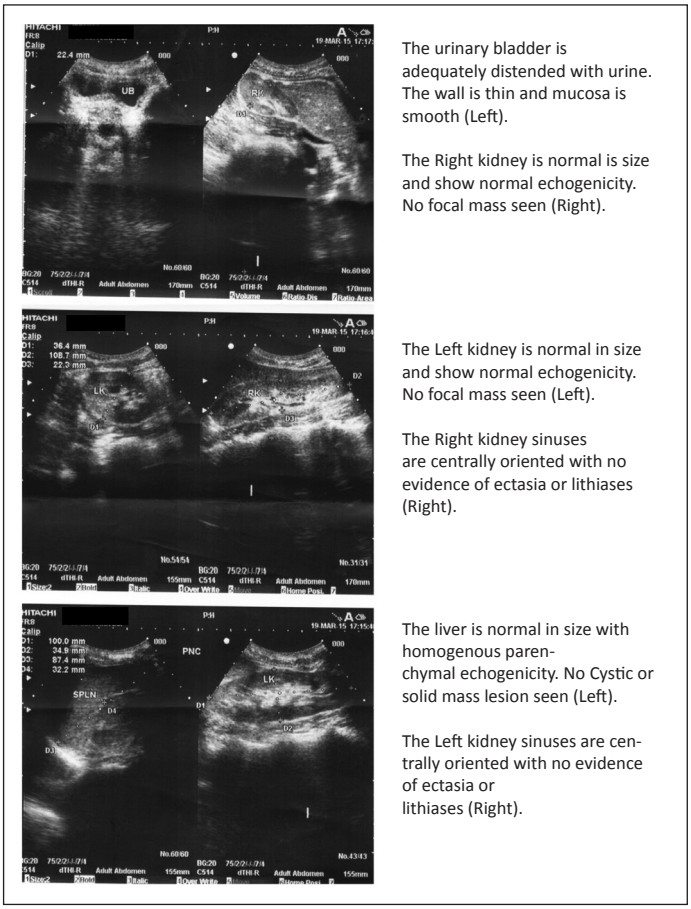


Figure 9. Karyotyping Test Result that shows patient have a 46XY Chromosome (March 6, 2015)



The urinary bladder is adequately distended with urine. The wall is thin and mucosa is smooth (Left).

The Right kidney is normal is size and show normal echogenicity. No focal mass seen (Right).

The Left kidney is normal in size and show normal echogenicity. No focal mass seen (Left).

The Right kidney sinuses are centrally oriented with no evidence of ectasia or lithiases (Right).

The liver is normal in size with homogenous parenchymal echogenicity. No Cystic or solid mass lesion seen (Left).

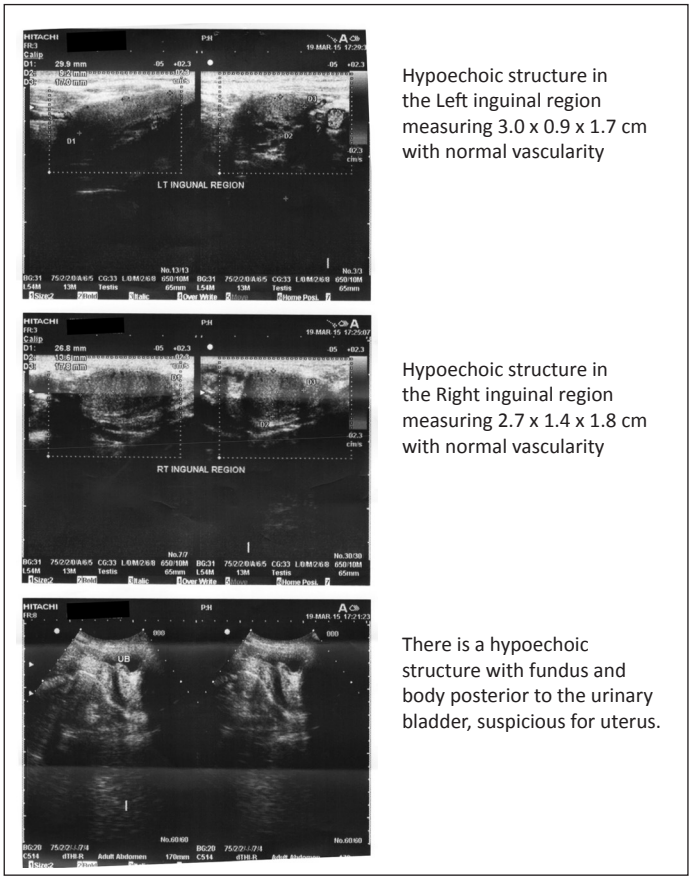
The Left kidney sinuses are centrally oriented with no evidence of ectasia or lithiases (Right).

Figure 10. Whole Abdominal Ultrasound Result (March 20, 2015)

Whole abdominal ultrasound showed hypoechoic solid structure with normal flow in the bilateral inguinal regions suggestive of bilateral testis, measuring 2.7 x 1.4 x 1.8 cm and 3.0 x 0.9 x 1.7 cm in the right and left inguinal region. There was also a tubular hypoechoic structure behind the urinary bladder suspicious for uterus, and a dedicated TVS or TRS was suggested. Small gallbladder polyps also noted. No gross pathology seen in the liver, pancreas, spleen, kidneys and urinary bladder (Figures 10, 11 & 12).

Transvaginal ultrasound was done and the previously mentioned tubular hypoechoic structure behind the bladder seen on whole abdominal ultrasound was noted to be blood vessels upon color Doppler (Figure 13). Patient was referred to Urology department for Bilateral Orchiectomy and supportive psychotherapy was given by Psychology department prior to Orchiectomy.

Patient was scheduled to undergo Cystoscopy and Bilateral Orchiectomy. Cystoscopy prior to definitive surgerywas performed to check for the presence of prostate, and other male internal genitalia. Cystoscopy showed absence of urethral and ureteral stricture and absence of prostate. No masses were also noted inside

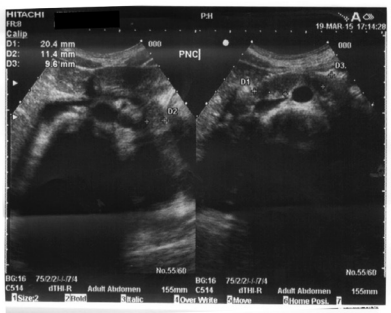


Hypoechoic structure in the Left inguinal region measuring 3.0 x 0.9 x 1.7 cm with normal vascularity

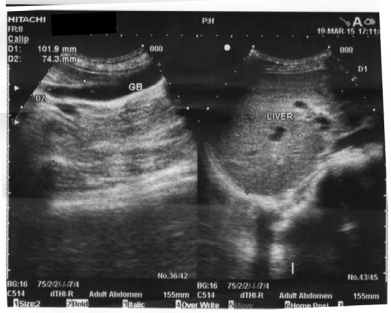
Hypoechoic structure in the Right inguinal region measuring 2.7 x 1.4 x 1.8 cm with normal vascularity

There is a hypoechoic structure with fundus and body posterior to the urinary bladder, suspicious for uterus.

Figure 11. Whole Abdominal Ultrasound (March 20, 2015)



The pancreas is normal in size and parenchymal echogenicity. No focal mass lesion seen



The gallbladder measures 5.4 x 2.4 cm in its widest diameter. There are at least two small hyperechoic lesion, the largest measuring 0.3 cm adherent to the gallbladder wall (Left).

The liver is normal in size with homogenous parenchymal echogenicity. intrahepatic biliary radicles and portal vein are not dilated (Right).

Figure 12. Whole Abdominal Ultrasound (March 20, 2015)

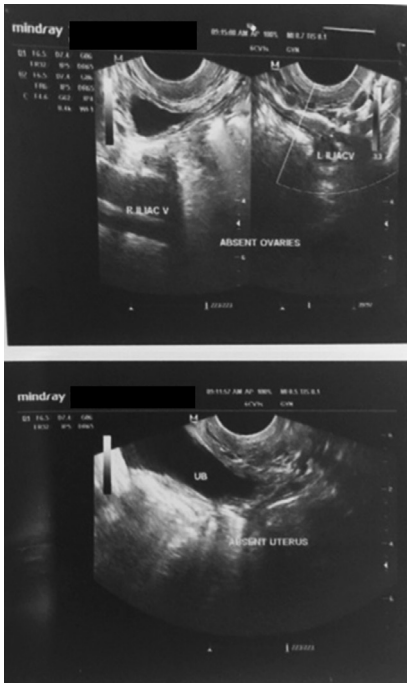


Figure 13. Transvaginal ultrasound result shows absent of ovaries (above) and absent of uterus (below) (April 16, 2015)

the bladder. On inguinal exploration the right testes was located at the right inguinal area measuring 6.0 x 3.3 x 2.5 cm (Figure 15). Left testes was noted at the left inguinal area measuring 6.5 x 4.0 x 2.5 cm (Figure 16). Both testes were removed. On inspection of the specimens, both testes were grossly normal. Cut section did not show a mass or areas of necrosis. Specimens were sent for histopathology examination.

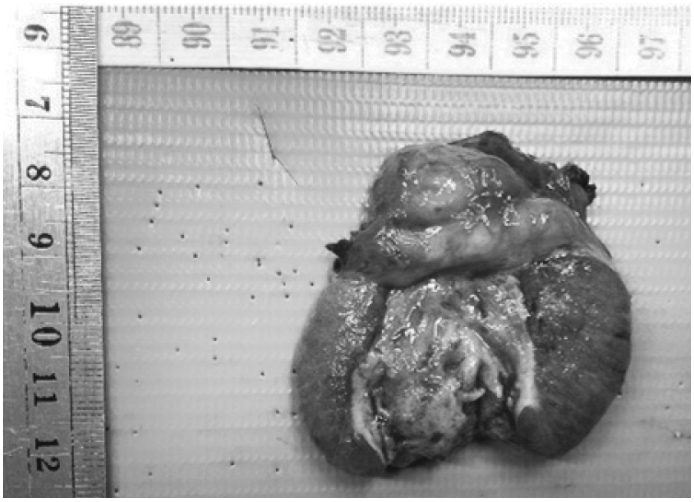


Figure 15. Right testis

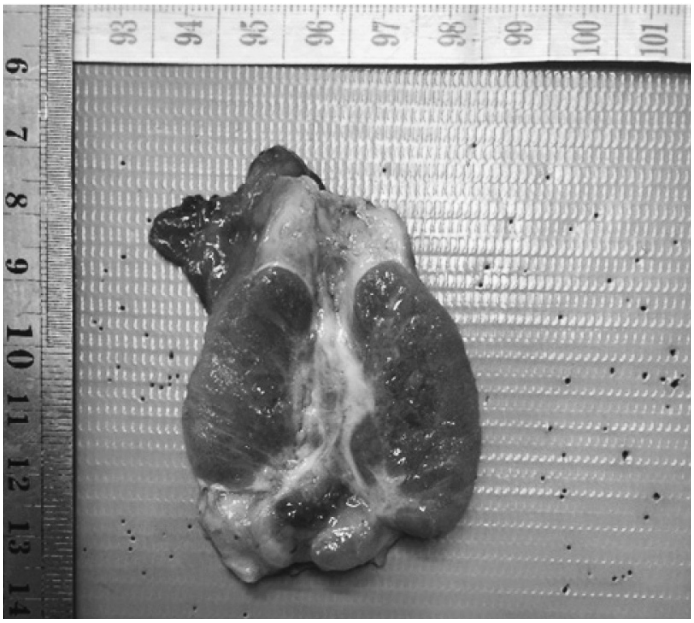


Figure 16. Left testis

Histopathology examination results revealed:

1. Athropic Testes Bilateral (Figures 17 and 18)
2. Unremarkable Epidydymis, Bilateral (Figures 19 and 20)
3. Unremarkable spermatic cord and vas deferens, Bilateral (Figures 21 and 22)

On follow up 2 weeks after orchiectomy, the patient was started on estrogen replacement therapy using Oestrodose 1 pump once a day, Calcium with Vitamin D supplementation and exercises were advised to prevent osteoporosis. Psychological counselling was also advised but patient was unable to comply since the patient wanted to go back to her province even though patient was instructed to come back for follow up. The time of writing of this paper, patientshowed acceptance on the diagnosis of AIS with no signs of depression.

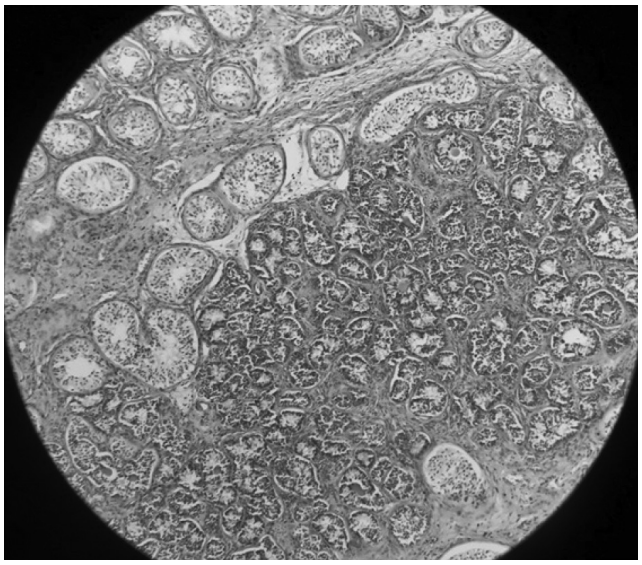


Figure 17. Microscopic slide showing atrophic right testis on low power magnification 10x

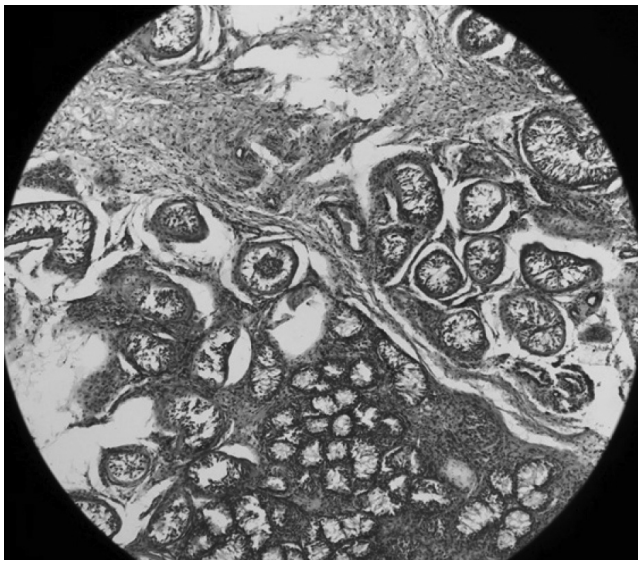


Figure 18. Microscopic slide showing atrophic left testis on low power magnification 10x

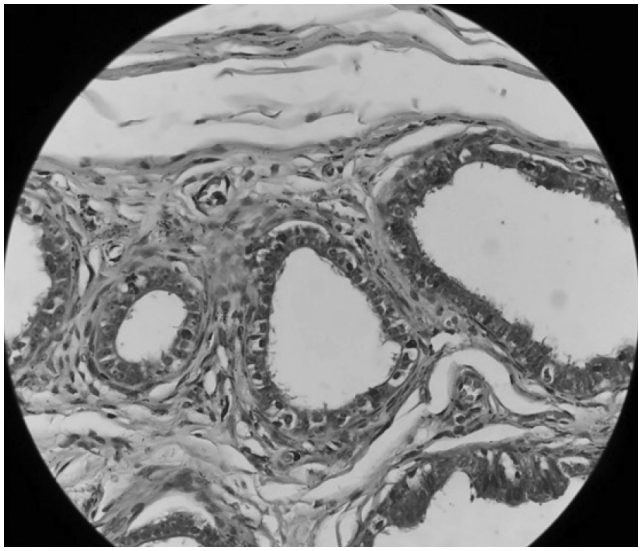


Figure 19. Microscopic slide showing right epididymis on low power magnification 10x.

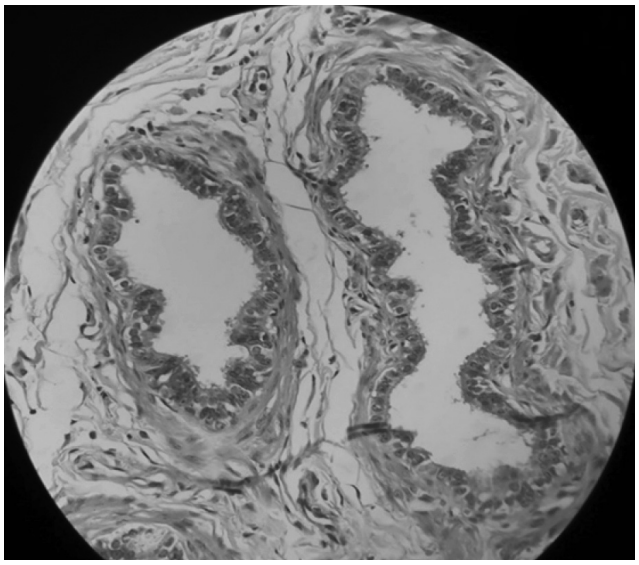


Figure 20. Microscopic slide showing left epididymis on low power magnification 10x.

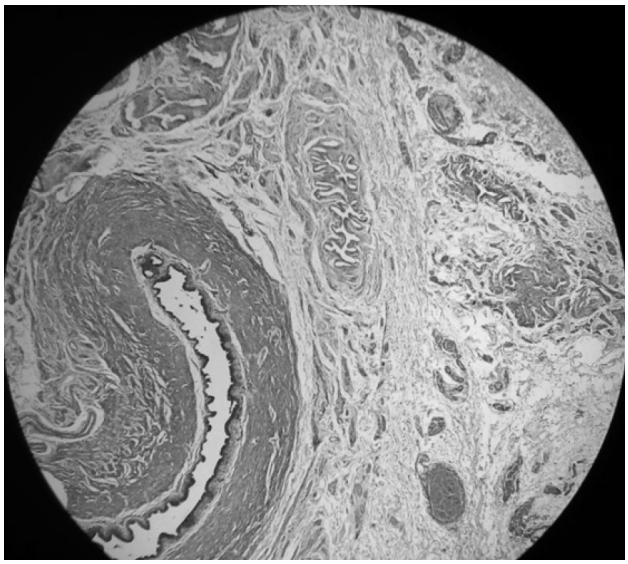


Figure 21. Scanner view of right spermatic cord and right vas deferens

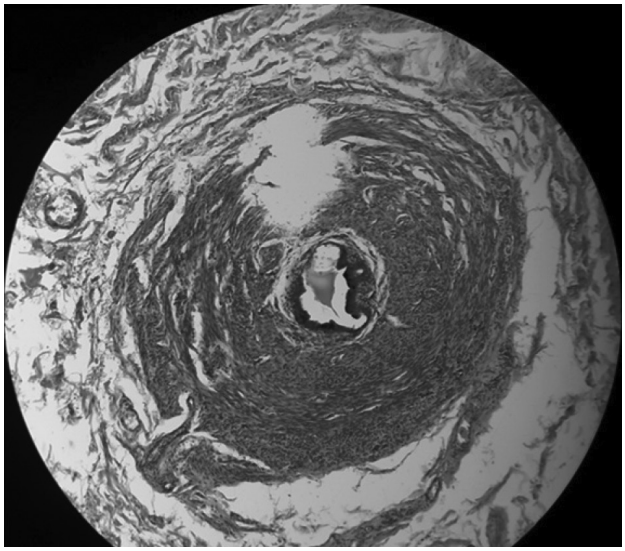


Figure 22. Scanner view of left spermatic cord and left vas deferens

DISCUSSION

This paper presented a case of 25 years-old, nulligravid, with primary amenorrhea. Patient has breast development with a tanner stage V and scanty pubic hair (Tanner Stage II). Axillary hair was absent (Table 1). Ultrasound was done revealing that the patient has absent uterus and ovaries with cervix not visualized. With this clinical presentation, Androgen Insensitivity Syndrome versus Mullerian Agenesis were considered. Serum testosterone was done with a result of elevated testosterone level. Karyotyping was also done and the result is 46XY which leads to the diagnosis of Androgen Insensitivity Syndrome.

Patient was classified as CAIS with grade 7 of Quigley AIS Clinical Classification (Table 2) since she has a normal female external genitaliawith no axillary hair and scanty pubic hair.[24]

In the investigation of primary amenorrhea, presence of secondary sexual characteristics are noted. If the breast is present and uterus absent, a karyotype analysis would confirm the diagnosis of AIS with the karyotype of XY as opposed to mullerian agenesis with an XX karyotype. Since the normal testosterone are produced; however due to mutation in the androgen receptors, the development of male gonads does not occur; this testosterone are converted to estradiol by aromatase enzyme for the development of the breast [14].

Women with CAIS have been shown to have decreased bone density[15]. Therefore it is important to know the timing of doing gonadectomy. A substantial bone loss occurs after gonadectomy. Adequate estrogen replacement during late adolescence and in the twenties will help build bone density and help in maturation of secondary sexual characteristics. However these patients need to be maintained on calcium and vitamin D as well as to do regular weight bearing exercise. DEXA scanning to examine bone mineral density should be instituted in regular basis.

The risk of gondal malignancy is believed to be lower in CAIS compare to PAIS by 5%[16]. Morris and Mahesh reported a 22% incidence of malignant gonadal tumors in 181 AIS patients. Majority of malignancies were of germ cell origin[17]. Tumors prior to puberty are rare, however, the incidence rise 3.4% at age of 25 and reach 33% by age of 50[18]. Gonadectomy and hormone therapy (physiologic estrogen treatment) generally are best delayed until after pubertal development is complete, by approximately age 16-18.[32]

Our patient presented with weight loss of 10 kg in 5 years, making us consider a possibility of malignancy versus hyperthyroidism thus a thyroid function test was requested to rule out hyperthyroidism.

Approximately 5% of all dysgerminomas are associated with CAIS, XY gonadal dysgenesis, and 45, XO, 46, XY mixed gonadal dysgenesis[19]. Due to these incidence rates, the current recommendation is for removal of gonads after puberty. Because the gonads are frequently located along the pelvic sidewall, the surgery closely resembles a bilateral oophorectomy. At times just like in our patient, the gonads will have descended into the inguinal, a general surgery or urology consult is indicated in these situations. Hormonal supplementation, most easily supplied through oral or transdermal estrogen, should be given after gonadectomy.

Not like most of the AIS patients, in this case, the patient has a vaginal canal that measures 7 cm, which is the same length of normal vagina. Patient had her first sexual contact when she was 22 years and claims to have no difficulty in sexual contact. There is no need for vaginal creation in this case since the patient has a normal functional vagina.

Concerns should be addressed on how they behave with the society, their relationship, infertility. Therefore, the psychological aspect in management of AIS should start when the condition is recognized. The management should not focus on the individual itself, but also the whole family. Counselling should be offered in this kind of patient. It is often that psychological counselling is an important factor in treating AIS especially preparing the patient who will undergo surgery.[21]

One legal aspect of importance is gender determination. There were no documented cases of self-reassignment gender determination in AIS case.[21] The most important legal factor is the sex assigned by the birth attendant. Article 408 of the civil code in Philippines clearly stated the gender of the newborn child as requirement for registration of birth. In AIS cases, one may appear as a woman; however she has an internal reproductive system of a man. 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 made, a petition to the court should be made to correct the entry in the birth certificate of AIS patient. Philippine constitution based on article 1 of family code; only recognize marriage between a man and a woman.[22] The confusion on marital status of affected AIS patient may arise. Our patient has a secondary characteristic of a woman and she also plays a role as a woman in her daily life. She has living partner, however, they do not have plan to get married in nearby future. However, legal complication of AIS needs further clarification for there is yet not court action filled in the Philippines to determine validity of marriage involving couple affected by AIS.

An issue of disclosure or truth telling is an integral part of management of AIS as AIS is known as impossible

Table 1. Classification of Breast Growth and Pubic Hair Growth[25]

Classification	Description
Breast Development	
Stage 1	Elevation of papilla only
Stage 2	Elevation of breast and papilla as small mound, increase areola diameter
Stage 3	Further enlargement without separation of breast and areola
Stage 4	Secondary mound of areola and papilla above the breast
Stage 5	Recession of areola to contour of the breast
Pubic Hair Development	
Stage 1	No pubic hair
Stage 2	Sparse, long, pigmented hair, primarily on labia majora
Stage 3	Dark, coarse, curled hair sparsely distributed over mons
Stage 4	Adult-type hair, abundant but limited to the mons
Stage 5	Adult type hair, extending onto the medial thigh

for child bearing. If the patient is diagnosed to have AIS during infancy, then the family of the patient and usually the doctor need to talk when to disclose the information to the patient, however when the diagnosis is made when the patient is an adolescent, then the information usually are told immediately to the patient [31].

A multidisciplinary approach is mandatory for support, coping strategies, correct sex of rearing, and long term follow up in management of AIS.

SUMMARY

This a case report of a 25-year-old with complete androgen insensitivity syndrome. Patient came to our institution with chief complaint of primary amenorrhea and presented as phenotypically female with no axillary hair, scanty pubic hair, normal external female genitalia and bilateral inguinal masses. Transvaginal ultrasound revealed absent of uterus and bilateral ovaries. Karyotyping result of XY lead to the diagnosis of Complete AIS. Gonadectomy was performed followed by esterogen replacement therapy, and supplementation of calcium plus vitamin D. Psychological support was initially started upon pre-operative diagnosis of CAIS. However, post-operative follow up with psychiatry department was unable to comply since patient went back to her province.

As to the time of writing this paper, and upon follow up with REI section, patient was noted to show acceptance of her condition with no signs of depression noted. ■

Table 2. Quigley clinical classification of androgen insensitivity syndrome[24]

Grade		Genital appearance and clinical features
Grade 1	MAIS	Male genitals, infertility
Grade 2	PAIS	Male genitals but mildly 'under-masculinized', isolated hypospadias
Grade 3	PAIS	Predominantly male genitals but more severely 'under-masculinized' (perineal hypospadias, small penis, cryptorchidism i.e. undescended testes, and/or bifid scrotum)
Grade 4	PAIS	Ambiguous genitals, severely 'under-masculinized' (phallic structure that is indeterminate between a penis and a clitoris)
Grade 5	PAIS	Essentially female genitals (including separate urethral and vaginal orifices, mild clitoromegaly i.e. enlarged clitoris)
Grade 6	PAIS	Female genitals with pubic/underarm hair
Grade 7	CAIS	Female genitals with little or no pubic/underam hair

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