Coping up with an Abnormal Chromosome: The Role of the Gynecologist in the Management of Complete Androgen Insensitivity Syndrome*

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Androgen insensitivity syndrome is a rare X-linked recessive androgen receptor defect seen in 1-5 of 100,000. It occurs in phenotypically normal women with adequate breast development, normal external genitalia, a vagina of variable depth, absent uterus, and sparse or absent pubic hair and axillary hair. These patients have male karyotype (XY) and the gonads may be intra-abdominal, inguinal, or labial.

This is a case of a 25-year old phenotypic female with primary amenorrhea, bilateral inguinal masses and a 46, XY karyotype. Following the diagnosis of complete androgen insensitivity syndrome, a multidisciplinary team, with the gynecologist as the primary physician, was formed. She underwent bilateral gonadectomy and was given continuous estrogen therapy and calcium supplementation. Pre-operative and post-operative supportive psychotherapy and continuous psychosocial support from her family and online AIS support groups played a major role in the positive adaptation of the patient.

Key words: androgen insensitivity syndrome (AIS), complete androgen insensitivity syndrome (CAIS)

Introduction

A person's sexuality is influenced by different chromosomal, genetic, hormonal, gonadal, genital and psychological attributes.[1] The complex interaction of these factors determine a person's behavior and social role. Problems in sexual identity may arise when there are discordances among these six aspects, such as often encountered in patients with disorders of sex development.

Disorders of sex development (DSD) occur with an incidence of 1:4,500 to 1: 5,000 live births. A DSD is defined as a congenital condition in which the chromosomal, gonadal, or anatomical sex is atypical. DSDs can be subdivided into three main groups: 1) disorders associated with gonadal dysgenesis, 2) conditions associated with prenatal, and possibly also postnatal, virilization of 46, XX subjects, and 3) and disorders associated with undervirilization of 46, XY individuals,[2] such as those having androgen insensitivity syndrome.

Androgen insensitivity syndrome (AIS) is a rare inherited form of male pseudohermaphroditism that occurs in phenotypically normal women with adequate breast development, normal external genitalia, a vagina of variable depth, absent uterus, and sparse or absent pubic hair and axillary hair. These patients

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have male karyotype (XY) and negative sex chromatin. The gonad may be intra-abdominal, inguinal, or labial.[3]

Androgen insensitivity syndrome is a rare X-linked recessive androgen receptor defect seen in 1–5 of 100,000.[4-7] In the Philippines, incidence of AIS is unknown. Seven cases of AIS have been reported in the Philippine Obstetrical and Gynecological Society database from 2005 to 2014, five of which have been published in the Philippine Journal of Obstetrics and Gynecology and Philippine Journal of Reproductive Endocrinology and Infertility.[1,8-11] This is the second case of AIS in our institution. The first case was reported in 2012.[10]

This paper presents the case of a 25-year old phenotypic female with bilateral inguinal masses and an XY karyotype. Specific objectives are the following:

1) to briefly review the pathophysiology, clinical presentation and diagnosis of complete androgen insensitivity syndrome (CAIS),

2) to discuss the role of the gynecologist in the medical and surgical management and psychosocial adjustments of women with CAIS

3.) to emphasize the need for social support to help women diagnosed with CAIS cope with and accept their condition.

The Case

R.P. is a 25-year old individual with late diagnosis of Disorder of Sex Development (DSD) with female-oriented psychosocial rearing. She is phenotypically female who first consulted a gynecologist at 16 years old due to primary amenorrhea and left inguinal mass. Ultrasound was requested but was not done due to financial constraints. The patient remained amenorrheic. At 21 years old, another mass at the right inguinal area was noted, associated with a 4-kg weight loss in 1 year. She only consulted a surgeon at 25 years old. Inguinal ultrasound revealed nodules in both inguinal regions which may represent lymph nodes and a left inguinal hernia. Chest X-ray was normal. No uterus and cervix were demonstrated by vaginal sonography. Bilateral small ovaries were noted. She was subsequently referred to our institution.

Past medical history was unremarkable. There were no heredo-familial diseases noted such as hypertension, diabetes, asthma, cancer, thyroid and kidney diseases. There was also no family history of sexual ambiguity, sterility or primary amenorrhea. Patient is the 3rd in a brood of seven. Patient's eldest sister has 4 children, her eldest brother has 2 children and her other younger sisters have regular menstrual cycles. Patient is a non-smoker, a non-alcoholic beverage drinker and is currently unemployed. Coitarche was at 22 years old with 1 sexual partner and is currently in a monogamous relationship. She has no sexual difficulties such as dyspareunia, vaginismus, arousal and orgasm disorders.

On physical examination, patient stood at 165 cm with lean and long limbs and a BMI of 15.6 kg/m$^{2.}$ Vital signs were stable with no laryngeal prominence and anterior neck mass. There was no axillary hair and breasts were grossly normal at Tanner stage V (Figures 1, 2). There were 2 movable, non-tender, reducible inguinal masses, measuring 4 cm x 3.5 cm on the right and 5 cm x 3 cm on the left (Figure 3).

Figure 1. Absence of axillary hair and no laryngeal prominence.

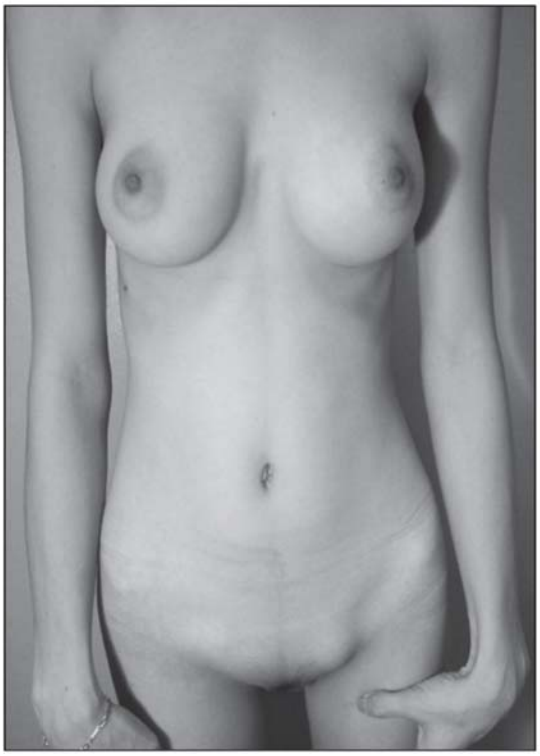

Figure 2. Fully developed breasts at Tanner V.

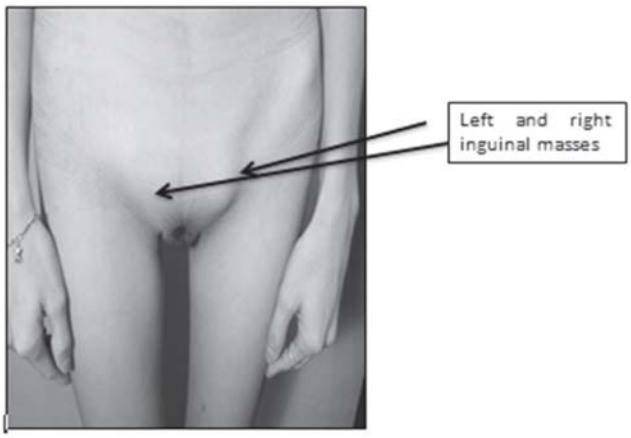

Figure 3. Visible bilateral inguinal masses

Examination of the external genitalia revealed pubic hair at Tanner stage 2, normal looking clitoris, labia majora and minora, and a small urethral opening (Figure 4). Speculum examination showed a pinkish vaginal mucosa, vaginal canal measured 6 cm and the vagina ended in a blind pouch with no appreciable cervix (Figures 5, 6). On internal examination, the vagina admits 2 fingers with ease, vaginal canal measures 6 cm with no palpable cervix, uterus nor adnexae. Rectovaginal examination findings were consistent with internal examination findings.

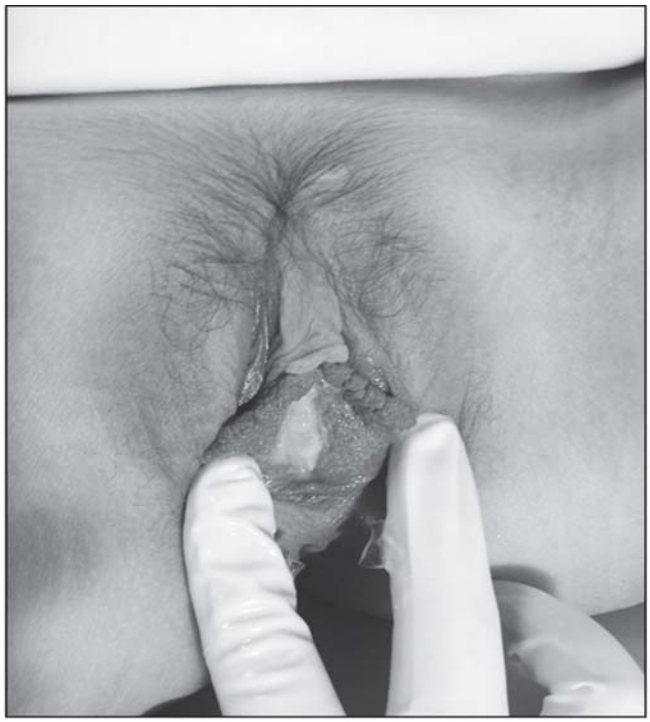

Figure 4. Pubic hair at Tanner II with normal-looking clitoris, labia majora and labia minora.

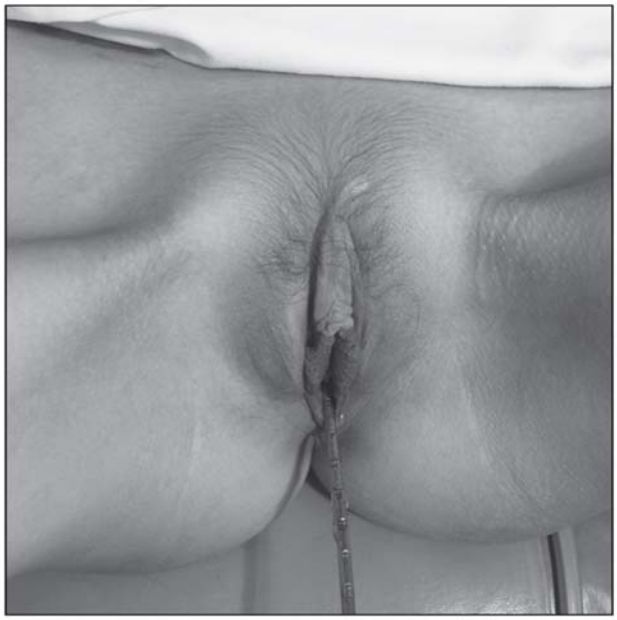

Figure 5. Vaginal canal length of 6 cm.

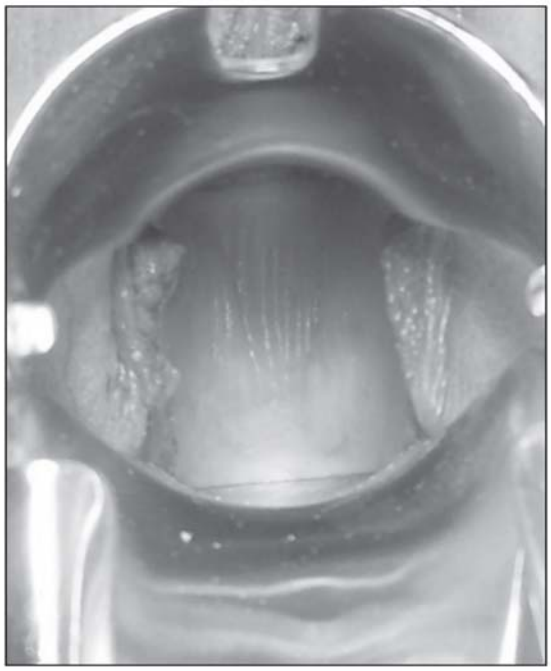

Figure 6. Vagina ending in a blind pouch.

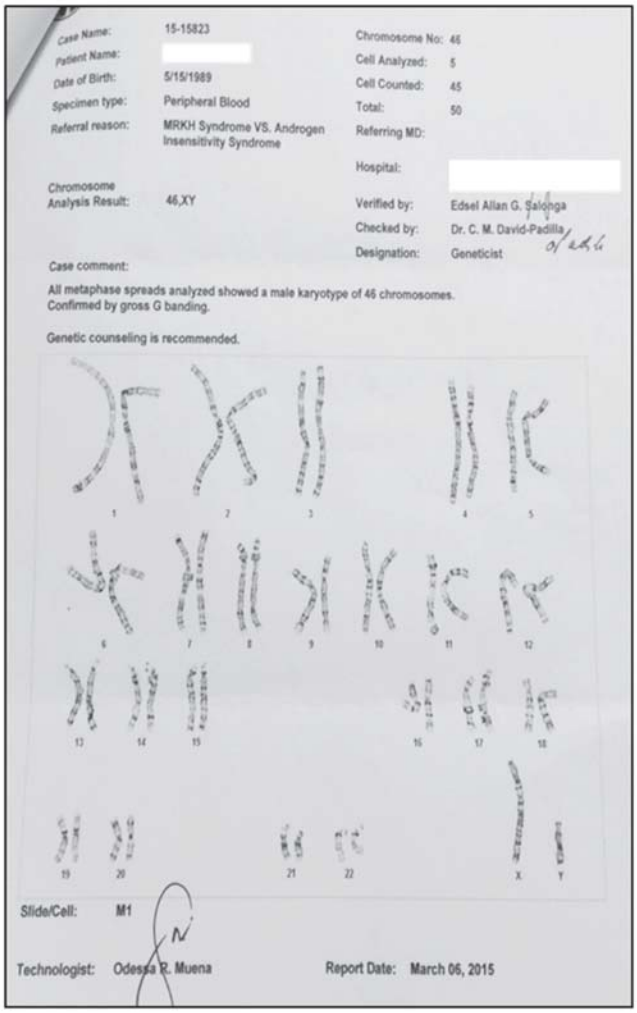

Figure 7. Karyotyping result of 46, XY.

Thyroid function tests were normal. The serum testosterone was > 52.05 nmol/L, above the normal values for both males and females. Chromosomal analysis was 46, XY karyotype (Figure 7).

Whole abdominal ultrasound showed hypoechoic solid structures with normal flow in the bilateral inguinal regions suggestive of bilateral testis (Figure 8). There was also a tubular hypoechoic structure behind the urinary bladder suspicious for uterus, and a dedicated TVS or TRS was suggested (Figure 9). Small gallbladder polyps were also documented. No gross pathology was seen in the liver, pancreas, spleen, kidneys and urinary bladder. 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. The uterus and the ovaries were also absent on transvaginal ultrasound (Figures 10,11).

Disclosure of the diagnosis of androgen insensitivity syndrome was made, and gender assignment as female following the patient's sex of rearing and counselling were provided. Patient was encouraged to check the websites aissg.org and aisdsd.org and be part of the online AIS support groups. Patient was also referred to Psychiatry department for supportive psychotherapy and to the Urology department for bilateral orchiectomy.

Cystoscopy prior to definitive surgery was performed to check for the presence of prostate and other male internal genitalia. Cystoscopy showed absence of urethral and ureteral strictures and absence of prostate. No masses were also noted inside the bladder. On inguinal exploration, the right testis was located at the right inguinal area measuring 6.0 cm x 3.3 cm x 2.5 cm. Left testis was noted at the left inguinal area measuring 6.5 cm x 4.0 cm x 2.5 cm. Bilateral testes were removed and both were grossly normal (Figures

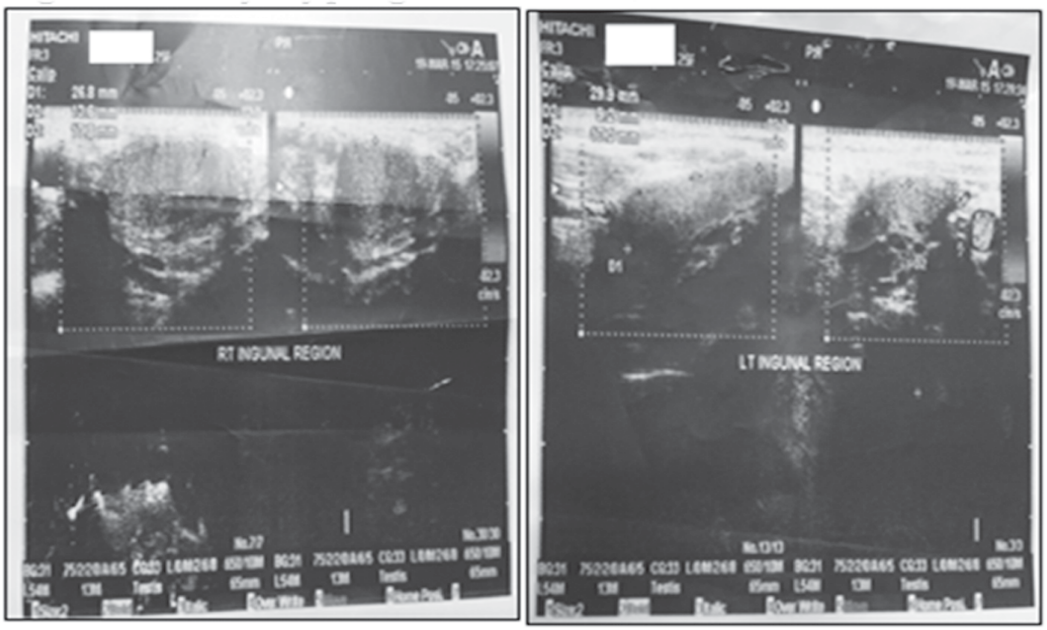

Figure 8. Ultrasound image of right and left inguinal regions.

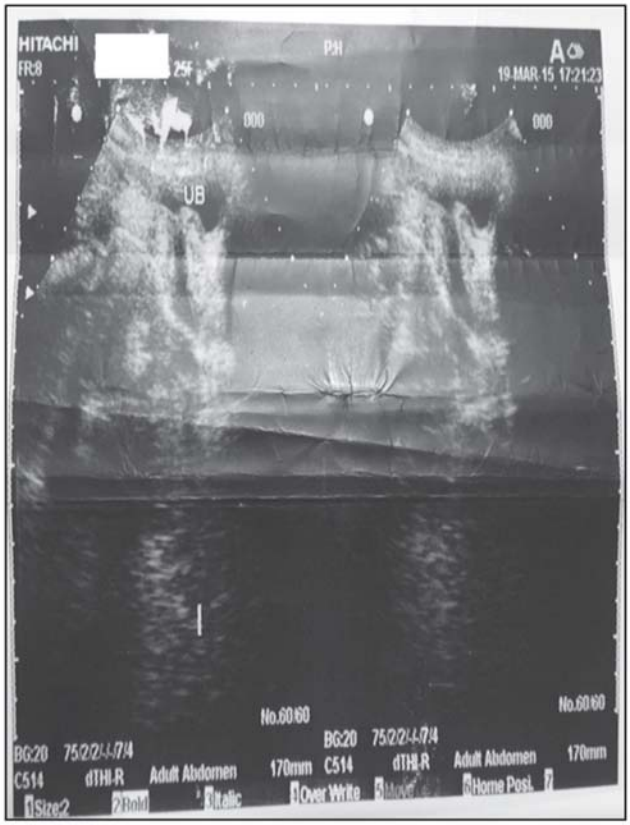

Figure 9. Ultrasound image of the tubular structure behind the urinary bladder.

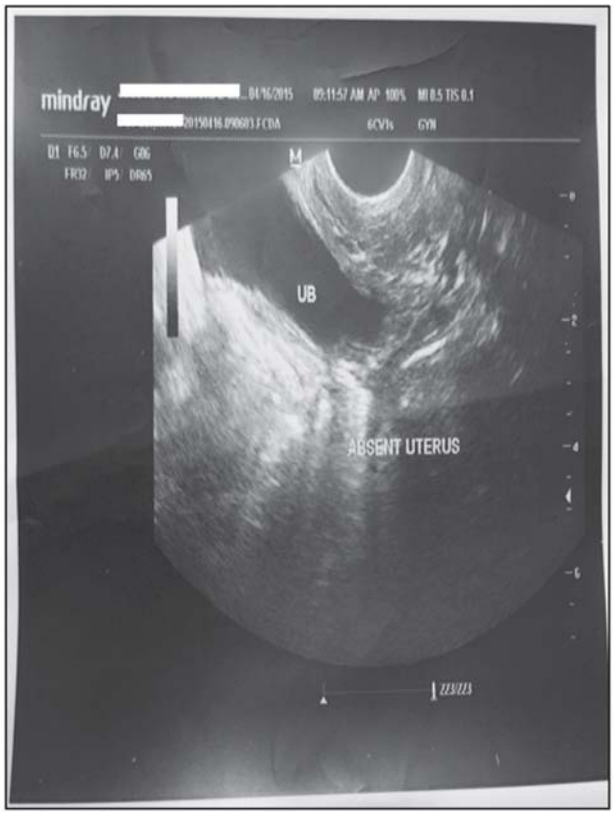

Figure 10. Absent uterus noted on transvaginal ultrasound.

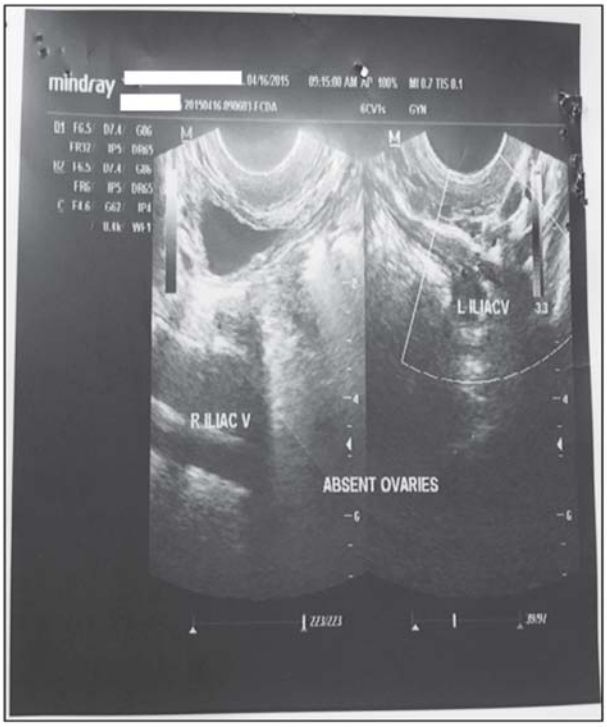

Figure 11. Transvaginal ultrasound image of absent bilateral ovaries.

12). Histopathology examination results revealed atrophic bilateral testes, unremarkable bilateral epididymis, and unremarkable bilateral spermatic cord and vas deferens (Figures 13-15).

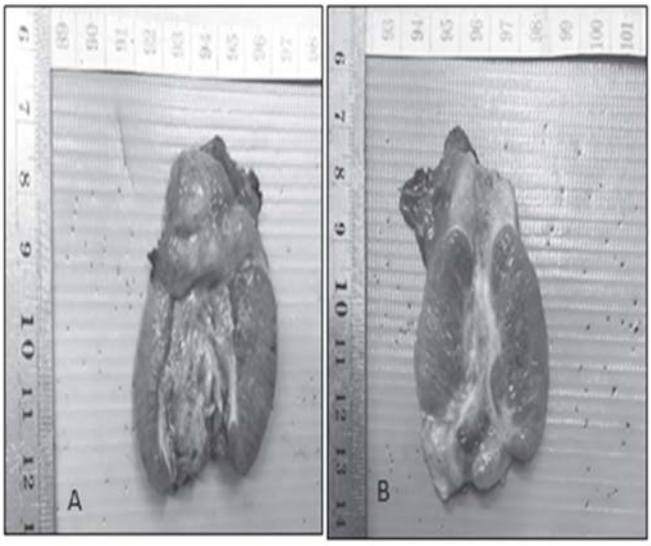

Figure 12. Cut sections of the right (A) and left (B) testis.

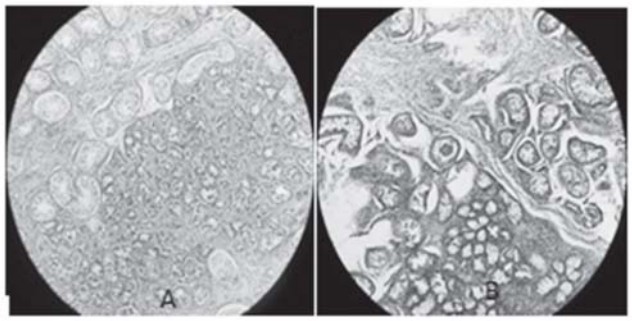

Figure 13. Microscopic slide showing atrophic right (A) and left (B) testis on low power magnification 10x.

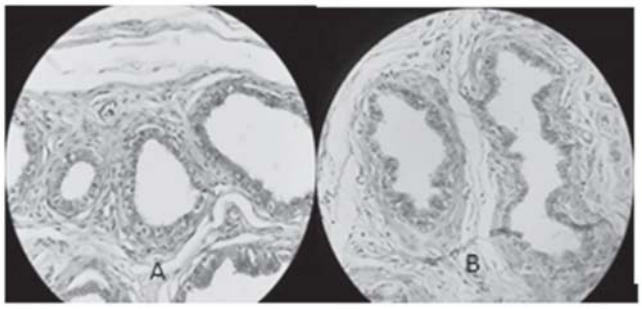

Figure 14. Microscopic slide showing right (A) and left (B) epididymis on low power magnification 10x.

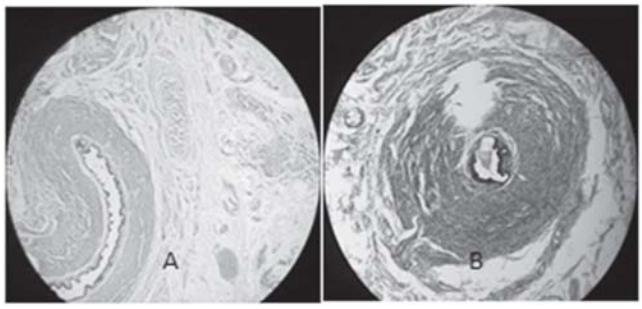

Figure 15. Scanning view of right (A) and left (B) vas deferens.

On follow-up 2 weeks after orchiectomy, estrogen replacement therapy was started using 17β-estradiol transdermal gel at 0.75mg/day. Calcium with Vitamin D supplementation was also commenced and exercises were advised to prevent osteoporosis. Supportive psychotherapy with Psychiatry department and online interaction with members of AIS support groups were continued. On follow-up two months after bilateral

orchiectomy, patient showed acceptance of the diagnosis of AIS, with positive outlook in life and with no signs of depression. The patient and her boyfriend have plans of marriage and adoption in the future.

Discussion

Primary amenorrhea is characterized by no menses by age 14 in the absence of growth or development of secondary sexual characteristics or no menses by age 16 regardless of the presence of normal growth and development of secondary sexual characteristics.[12]

When presented with primary amenorrhea, a comprehensive history and physical examination must be done, taking into account the presence or absence of secondary sexual characteristics (breasts development), and the presence or absence of internal genitalia (uterus). Thus, the findings in physical examination can alert the clinician to possible causes and indicate which laboratory tests should be performed.[13]

The patient in this study presented at adulthood with complaints of primary amenorrhea, bilateral inguinal masses and weight loss. Upon physical examination, patient is a phenotypic female with fully developed breasts at Tanner stage V and absent axillary hair and scant pubic hair at Tanner stage II. External genitalia were grossly female with a well-developed vaginal canal ending in a blind pouch. Internal examination and transvaginal ultrasound results confirmed absence of the uterus, ovaries and cervix. For a patient with fully developed breasts and absent uterus, two conditions should be considered: androgen insensitivity syndrome and mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome).

Mullerian agenesis is the second most common cause of primary amenorrhea, accounting for about 15% and occurs in 1 in 4,000 or 5,000 female births.[13] It results from failure of mullerian development, logically might be attributed to an activating mutation in the gene encoding antimullerian hormone (AMH) or its receptor, causing excessive AMH activity. Patients with mullerian agenesis typically present in late adolescence or as young adults, with primary amenorrhea as their only complaint. They exhibit normal, symmetrical breast and pubic hair development, no visible vagina, and have no symptoms of crytomenorrhea because the rudimentary uteri contain no functional endometrium.[14]

Patients with androgen insensitivity syndrome most commonly present after the age of puberty in late adolescence or as young adults with primary amenorrhea. They exhibit asymmetrical secondary sexual development (breast development with absent or scant pubic hair), a short vagina with no visible cervix, and have no other symptoms or complaints. AIS is the third most common cause of primary amenorrhea, after gonadal dysgenesis and mullerian agenesis.[12]

To differentiate mullerian agenesis from androgen insensitivity syndrome, serum testosterone and karyotyping should be requested. Patients with mullerian agenesis have normal female serum testosterone concentrations, and a 46, XX karyotype.[12] Laboratory results of our patient revealed an elevated serum testosterone and a 46, XY karyotype, thus ruling out mullerian agenesis and clinching the diagnosis of androgen insensitivity syndrome.

Androgen insensitivity syndrome was originally described by Morris in 1953 as the Syndrome of Testicular Feminization presenting as a phenotypic female with typical female body build, well-developed breasts, scanty or absent pubic and axillary hair, a small vagina ending in a cul-de-sac, absence of internal female structures and presence of testes intra-abdominally, in the inguinal canal or in the labia majora.[15] Patients with androgen insensitivity syndrome are chromatin negative and have XY karyotypes.[3] Therefore, genetically, they are males with testes that produce both testosterone and anti-mullerian hormone. However, an inactivating mutation in the gene encoding the intracellular androgen receptor (AR) results in an end organ insensitivity to androgen actions that prevents normal masculinization of the internal and external genitalia during embryonic development.[12]

Androgens exert their effects by mediating the differentiation and development of the normal male phenotype via a single receptor protein, the

androgen receptor (AR).[16] The androgen receptor belongs to the superfamily of nuclear receptors which includes receptors of other steroid hormones,[17] is expressed in fetal tissues as early as 8 weeks of gestation and is activated in a ligand-dependent manner to coordinate expression of suitably responsive genes. In the human male embryo, testes begin to secrete androgens at 9 weeks of gestation. Endogenous androgens, testosterone (T) and dihydrotestosterone (DHT) form a complex with AR, giving rise to different biological messages.[18] Testosterone, which peaks between 11 and 18 weeks of gestation, stimulates differentiation of the wolffian duct system into epididymis, vas deferens and seminal vesicles. Development of the prostate from the urogenital sinus and masculinization of the primordial external genital into penis and scrotum require the more potent androgen, DHT, originating from the action of the enzyme 5alpha-reductase type 2 on testosterone.[19]

Since the AR gene is located on the Xq11-12 chromosome, the syndrome is consequently an X-linked recessive disorder passed on from the unaffected mother, who is a carrier of the mutant gene. If a mother carries the defective androgen receptor gene on one of her X chromosomes, her risk of having a child that carries the defective gene is 50%. Half of these will have only one X chromosome and therefore express the recessive disorder.[20] Automated DNA sequencing of the coding region and splice sites of the androgen receptor gene is available in the United States and United Kingdom. A mutation is identified in more than 95% of patients with complete androgen insensitivity syndrome with transcriptional activity generally absent or severely impaired in studies of androgen-receptor mutations associated with CAIS. One thousand one hundred eleven mutations in different patients are entered in the Cambridge database of androgen receptor genes as of September, 2014.[21] Most mutations of the androgen receptor gene are located within the ligand- binding domain. The most common functional androgen receptor defect results from disruption of the hydrophobic ligand-binding pocket whereas about 30% of mutations are the result of sporadic anomalies.[22,23] If there are no mutations in the AR gene one could speculate that mutations in co-regulatory proteins could be the cause of disorder.[24]

The clinical phenotypes of AIS could vary and be grouped into three categories: complete AIS, partial AIS, and mild AIS. Literature review showed three classification systems for AIS with their respective phenotypes. In 1992, Griffin described a spectrum of androgen resistance syndromes ranging from the undervirilized male to 5a-reductase deficiency.[16] In 1995, Quigley, et al. presented a more detailed 7-grade classification of AIS according to the severity of androgen resistance.[25] Whereas in 1997, Sinnecker, et al. also published a classification scheme of androgen insensitivity syndrome.[26] Each classification will be presented.

Griffin described complete testicular feminization as those patients with absent mullerian and wolffian derivatives and with female breasts, external genitalia and urogenital sinus. Incomplete testicular feminization is characterized by absence of mullerian derivatives and presence of wolffian derivatives, female breasts and urogenital sinus derivatives, and posterior fusion and clitoromegaly. Reifenstein's syndrome is described as absence of mullerian derivatives and presence of gynecomastia, male wolffian derivatives, underdeveloped male urogenital sinus derivatives and perineoscrotal hypospadias. Infertile male or undervirilized male syndrome are likewise characterized by absence of mullerian derivatives and presence of gynecomastia, male external genitalia and male wolffian and urogenital sinus derivatives. Patients with absent mullerian derivatives, male breasts and wollfian derivatives, and female urogenital sinus derivatives and female genitalia that may virilize at puberty is classified as 5a-reductase deficiency (Table 1).[16]

Quigley, et al. specifically categorized the different phenotypes of AIS in 3 types namely complete AIS, partial AIS and mild AIS and sub-classified these into 7 grades according to androgen sensitivity. He further subdivided partial AIS according to the external genitalia as predominantly female, ambiguous genitalia and predominantly female. Complete AIS is categorized as grade 7 with female phenotype and absence of/scarce

Table 1. Clinical features of androgen resistance syndromes (adapted and modified from Griffin JE. Androgen resistance - the clinical and molecular resistance. New England Journal of Medicine. 1992; 326 (9): 611-618).

	Mullerian derivatives	Wolffian derivatives (epididymis, vas deferens, seminal vesicle)	Urogenital sinus derivatives (prostate and urethra)	External Genitalia (penis and scrotum)	Breasts
Undervirilized Male Syndrome	Absent	Male	Male	Male	Gynecomastia
Infertile Male Syndrome	Absent	Male	Male	Male	Gynecomastia in some
Reifenstein phenotype	Absent	Male	Under-developed Male	Perineoscrotal Hypospadias	Gynecomastia
Incomplete testicular feminization	Absent	Male	Female	Posterior fusion and clitoromegaly	Female
Complete testicular feminization	Absent	Absent	Female	Female	Female
5α-Reductase Deficiency	Absent	Male	Female	Female, (may virilize at puberty)	Male

pubic or axillary hair at puberty. Predominantly female partial AIS is described as having normal female genital phenotype with androgen-dependent pubic and/or axillary hair at puberty (grade 6) and essentially female phenotype with separate urethral and vaginal orifices but with mild clitoromegaly or small degree of labial fusion (grade 5). Ambiguous genitalia (grade 4) presents with severely limited masculinization with phallic structure indeterminate between clitoris and penis and the urogenital sinus with perineal orifice and labioscrotal folds. Predominantly male phenotype presents as male genitalia with perineal hypospadias, small penis, cryptorchidism and/or bifid scrotum (grade 3). Grade 2 classification is described as presence of male genitals with mildly defective fetal masculization, isolated hypospadias and/or micropenis. Mild AIS is characterized by infertility with azoospermia and reduced virilization at puberty (Table 2).[25] This heterogeneity in phenotypic expression of androgen insensitivity is partly explained by a variety of AR defects but individuals with identical mutations may display widely variable phenotypes both within and between affected families. In two hundred and sixty-three patients with partial AIS identified by Deeb et al. in the Cambridge Intersex Database who underwent androgen binding analysis in fibroblasts obtained from genital skin biopsies and mutational analysis of the AR, an external masculinization score (EMS) was used to quantify the degree of undermasculinization, They concluded that no precise relationship exists between genotype and phenotype in AIS, particularly in partial AIS.[27]

Sinnecker, et al. in 1997 described a more simplified yet comprehensive classification of AIS. This classification is being used in the International

Table 2. Clinical classification of androgen insensitivity syndrome (Adapted and modified from Quigley CA, Bellis AD, Marschke KB, El-Awady MK, Wilson EM, and French FS. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocrine Reviews 1995; 16 (3): 271-321).

Type of Androgen Insensitivity Syndrome	External genitalia	Grading	Genital appearance and clinical features
Mild Androgen Insensitivity Syndrome	Normal male	Grade 1	Infertility with azoospermia; reduced virilization at puberty
Partial Androgen Insensitivity Syndrome	Predominantly male phenotype	Grade 2	Male genitals but mildly defective fetal masculinization; isolated hypospadias and/or micropenis
		Grade 3	Predominantly male phenotype; perineal hypospadias, small penis, cryptorchidism i.e. undescended testes, and/or bifid scrotum
	Ambiguous phenotype	Grade 4	Severely limited masculinization; phallic structure indeterminate between clitoris and penis; urogenital sinus with perineal orifice and labioscrotal folds
	Predominantly female phenotype	Grade 5	Essentially female phenotype; separate urethral and vaginal orifices; mild clitoromegaly or small degree of labial fusion
		Grade 6	Normal female genital phenotype; androgen-dependent pubic and/or axillary hair at puberty
Complete Androgen Insensitivity Syndrome	Normal female	Grade 7	Female genital phenotype with absence of/scarce pubic or axillary hair at puberty

Androgen Receptor Gene Mutation Database. Complete AIS, synonymous with testicular feminization syndrome described by Griffin, is characterized as absent or rudimentary wolffian duct derivatives, absence or presence of epididymides and/or vas deferens, with inguinal, labial, or abdominal testes, short blind-ending vagina and scant or absent pubic and/or axillary hair. Sinneckers et al.'s classification of partial AIS is synonymous with incomplete AIS, and mild AIS is synonymous to undervirilized male syndrome in the classification of Griffin. Like Quigley, Sinnecker also classified partial AIS into three, namely: predominantly female, ambiguous genitalia, and predominantly male. Partial AIS with predominant female phenotype presents with inguinal or labial testes, clitoromegaly and labial fusion and distinct urethral and vaginal openings or a urogenital sinus. Partial AIS patients with ambiguous genitalia have microphallus (<1 cm) with clitoris-like underdeveloped glans, labia majora-like bifid scrotum, descended or undescended testes, perineoscrotal hypospadias or urogenital sinus and gynecomastia in puberty. Partial AIS with predominantly male external genitalia have simple or severe isolated hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis, bifid scrotum, and either descended or undescended testes. Mild AIS presents with impaired spermatogenesis and/or impaired pubertal virilization and gynecomastia in puberty (Table 3).[26]

Table 3. Clinical classification for complete androgen insensitivity syndrome (Adapted from Sinnecker GH, Hiort O, Nitsche EM, Holterhus PM, Kruse K;German Collaborative Intersex Study Group. Functional assessment and clinical classification of androgen sensitivity in patients with mutations of the androgen receptor gene. Eur J Pediatr 1997;156(1):7-14).

Type	External Genitalia (Synonyms)	Findings
Mild Androgen Insensitivity Syndrome	Male ("undervirilized male syndrome")	• Impaired spermatogenesis and/or impaired pubertal virilization • Gynecomastia in puberty
Partial Androgen Insensitivity Syndrome	Predominantly female ("incomplete AIS")	• Inguinal or labial testes • Clitoromegaly and labial fusion • Distinct urethral and vaginal openings or a urogenital sinus
	Ambiguous	• Microphallus (<1 cm) with clitoris-like underdeveloped glans; labia majora-like bifid scrotum • Descended or undescended testes • Perineoscrotal hypospadias or urogenital sinus • Gynecomastia (development of breasts) in puberty
	Predominantly male	• Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis, bifid scrotum, and either descended or undescended testes • Gynecomastia in puberty
Complete Androgen Insensitivity Syndrome	Female ("testicular feminization")	• Absent or rudimentary wolffian duct derivatives • Absence or presence of epididymides and/or vas deferens • Inguinal, labial, or abdominal testes • Short blind-ending vagina • Scant or absent pubic and/or axillary hair

A mutation in the androgen receptor (AR) gene is detected in more than 95% of women with CAIS.[28] It can result from a wide variety of inactivating mutations in the AR gene, including major gene deletions, premature stop codons, splicing abnormalities, and missense mutations that result in amino acid substitutions in the androgen receptor. The receptor defects result in insensitivity to androgens. Androgen-induced wolffian duct development cannot proceed normally and the presence or absence of wolffian duct derivatives (epididymis, vas deferens) varies with the type of mutation. Remnants can be observed (adjacent to the testes) in those having point mutations in the ligand-binding domain of otherwise normally expressed receptors, which may permit a very limited response to high local androgen concentrations in utero.[12] This could explain the presence of epididymis and vas deferens on our patient. The lack of of the effect of dihydrotestosterone on the virilization of the urogenital sinus also resulted to clearly female external genitalia, absence of prostate and Tanner 2 pubic hair in our patient. The pubic hair of individuals with CAIS is often reported as 'scanty' or 'sparse.' It is unclear whether the hair that is present is anything more than the vellus hair (which is not androgen-dependent) similar to that found elsewhere on the body in both sexes at all ages or the androgen-dependent pubic hair. Quigley, et al. clarifies that true sexual hair – the longer, coarser, darker terminal hair characteristic of adult pubic and axillary regions – results from androgenic stimulation of hair follicles. The term pubic hair should therefore be confined to hair that is truly androgenic in nature, however sparse or

abundant, and its distribution should be described in terms of Tanner 3 staging.[29] Our patient presented with a Tanner stage 2 pubic hair, signifying absence of androgen response.

Our patient presented with breast development, female external genitalia with blind vagina pouch of normal length, absent uterus and fallopian tubes, bilateral inguinal masses and 46, XY karyotype. The gonads in 46, XY individuals will always be testes and can be found in any position, from the abdomen to the scrotum/labia majora, though they are most frequently found in the inguinal region probably because AMH normally mediates their descent.[12, 30] More than half of patients with CAIS have an inguinal hernia.[12,30] Grumbach and Conte also estimated the prevalence of AIS in phenotypically female infants presenting with inguinal hernia to be 1-2%.[31] At puberty, the breasts develop, driven by estrogen derived from the peripheral conversion of high circulating testosterone levels, unopposed by the actions of androgens.[12]

Patients with CAIS usually have shortened vagina with absent uterus and fallopian tubes. These mullerian derivatives are absent in our patient because the normal testes produce normal amounts of anti-mullerian hormone (AMH), which effectively suppressed mullerian development.[12] The vagina reflects the developmental contribution of the urogenital sinus, and in our patient, her vagina did not appear to be shortened but has attained an adequate length and distensibility since she has been sexually active for the past three years. The overall body habitus also is female, although the average height and weight of women with complete AIS is greater than that of normal women. Women with complete AIS also exhibit normal female sexual orientation and maternal instincts.[12]

Partial AIS with predominantly female external genitalia presents in a manner similar to CAIS; however, partial AIS with predominantly female external genitalia have signs of external genital masculinization including clitoromegaly or posterior labial fusion, and presence of androgen-dependent pubic hair with distribution described in terms of Tanner 3 staging.[26,32,33] Our case is a complete androgen insensitivity syndrome because the phenotype is female with female external genitalia having no signs of external genital masculinization, a Tanner stage 2 pubic hair, a genetic male with bilateral testes and with minimal wolffian structures. The definition of CAIS itself is controversial, with different authors expressing different views especially with regards to the presence or absence of wolffian duct derivatives. It is expected that with CAIS, wolffian duct derivatives would be absent as its development is dependent on androgen response. Griffin define CAIS as completely female external genitalia, paucity of axillary and pubic hair, and absent wolffian duct derivatives.[16] Quigley, et al. defines CAIS as completely female external genitalia without pubic hair, but states that remnants of wolffian duct derivatives may be found. Sinnecker et al. also stated that wolffian derivatives may be absent or present in CAIS. Bale also indicated that wolffian duct derivatives although rare, can also be found in women with CAIS.[34] Hannema et al. in 2006 investigated 44 CAIS patients with molecular pathological confirmation of an AR mutation and studied whether the presence of epididymis and/or vas deferens, previously shown to be associated with residual activity of mutant ARs, is related to a particular testicular phenotype. They concluded that 36% of these CAIS patients have epididymis and / or vas deferens.[35] Except for the recommendation of prepubertal gonadectomy for patients with partial AIS with predominantly female external genitalia to avoid the emotional discomfort of increasing clitoromegaly at the time of puberty,[33] the issues in the management of CAIS and partial AIS with predominantly female external genitalia are the same, hence the distinction from one another is purely academic. The management of partial AIS with ambiguous genitalia and those with predominantly male external genitalia is dependent on many factors and is beyond the scope of this paper, and from hereon, discussion shall focus on individuals with CAIS since our patient has the latter.

The hormonal profiles of patients with CAIS include elevated testosterone levels at the time of puberty. Elevated luteinizing hormone (LH) levels are also found, indicating androgen resistance at

the hypothalamic-pituitary level.[30] Concentrations of follicle stimulating hormone and inhibin are generally normal.[23] Our patient presented with a testosterone level above the normal ranges for both males and females. While it would have been interesting to note the LH, FSH and inhibin levels of our patient, their determination would have been purely academic and unnecessary to the definitive management since the patient's physical and genotypic manifestations were already characteristic of androgen insensitivity syndrome.[1]

Imaging studies can be employed in the diagnosis of CAIS. Transabdominal ultrasound can be used as a first-line examination for CAIS to assess the absence of mullerian structures and to locate the testes.[36] Since ultrasound is operator dependent and can remain inconclusive, magnetic resonance imaging MRI is the study of choice. MRI provides detailed anatomic information due to its superior tissue characterization and multiplanar capability. US and MRI have an equal sensitivity for depicting pelvic gonads, but MRI has higher sensitivity for the localization of intra-abdominal gonads.[37] MRI is the ideal imaging modality for our patient presenting with primary amenorrhea, bilateral inguinal masses and progressive weight loss. An ultrasound of the whole abdomen was performed instead due to financial constraints.

Management of androgen insensitivity syndrome should address functional, sexual, and psychological issues such as disclosure, gonadectomy and subsequent hormone replacement, creation of a functional vagina, and provision of genetic advice. Care needs to be individualized, flexible, and holistic. Management is dependent wholly on a multidisciplinary team with the inclusion of geneticists, neonatologists, endocrinologists, gynecologists, psychiatrists, surgeon and social workers in the team.[23]

Our patient presented with bilateral inguinal masses and progressive weight loss, making us consider hyperthyroididsm versus malignancy. Hyperthyroidism as the cause of weight loss was ruled out due to normal thyroid function test results. Knowing the 22% incidence of malignant gonadal tumors in 181 AIS patients as reported by Morris and Mahesh,[38] bilateral gonadectomy was recommended.

Gonadectomy is indicated because testes that are intraabdominal or that occur in the inguinal canal (such as in our patient) have an increased risk of developing a malignancy (gonadoblastoma or dysgerminoma), with an incidence reported to be approximately 20%.[13] The most frequent testicular tumor in AIS is seminoma.[23] It is believed to originate from the germinal epithelium of the seminiferous tubules. Other tumors, such as teratoma and testicular tubular adenoma (Sertoli cell tumor), have been reported.[39,40] In one early series of 50 cases, 11 malignancies, 15 adenomas, and 10 benign cysts were observed: a 22% incidence of malignancy and a 52% overall incidence of neoplasia.[12] Larger studies reveal that the risk in general may be as low as 0.8%.

Androgen insensitivity and increased estrogen levels in testis at puberty disturb the androgen/estrogen balance and probably aid tumor development, as seen in other tissues. The risk of tumor development increases with age, and carcinoma in situ can develop into malignant intratubular germ cell neoplasia. Seminoma usually occurs in the late 30s to early 50s. At 25 years of age the risk of testicular cancer has been estimated at 3.6%, which increases to 33% at 50 years of age.[20] Studies have suggested an increased tumor risk of greater than 30% in late adulthood if gonadectomy is not done and a review of the risk of adult women with complete androgen insensitivity syndrome having a gonadal tumor could not be more specific than 0–22%. Therefore, it is usually recommended that the gonads be left in place until after puberty is completed to allow full breast development and epiphyseal closure to occur. After these events occur, which is typically around age 18, the gonads should be removed.[13] If gonadectomy was not done in infancy, it is generally recommended to be performed in early adulthood to avoid the risk of gonadal tumors. The procedure is done laparoscopically if the gonads are intra-abdominal.[20] At times just like in our patient, the gonads will have descended into the inguinal area and a general surgery or urology consult was indicated.

Reconstructive vaginal surgery is rarely indicated for the creation of a functional vagina for CAIS patients. Vaginal dilators are an effective first-line treatment; some women achieve a similar effect with sexual intercourse. Adults with CAIS rarely report sexual problems (although little evidence exists) once a reasonable vaginal length has been achieved. If surgery is needed, it should be delayed until consent is given and the woman is able to manage dilator therapy herself after surgery.[20] While vaginal lengthening is needed for penile penetration in some women with CAIS, others have a normal vaginal length and report satisfactory intercourse despite never having received dilatation or surgery, such as in our patient as she has been sexually active for three years now. Three studies of orgasmic function report that women with CAIS can reach sexual climax indicating that androgens are not necessary for this aspect of sexuality in this group.[20] Contrary to some literature in which CAIS patients may have low libido or hyposexual function, our patient does not have any complaints of sexual difficulties.

Estrogen therapy following gonadectomy is indicated for our patient to maintain secondary sexual characteristics and to prevent osteoporosis and cardiovascular diseases.[20] Several studies have reported osteopenia in women with CAIS.[41] Decreased bone mineral densities in the lumbar spine and hip regions occur both prior to gonadectomy in women with CAIS as well as in gonadectomized women receiving daily estrogen therapy. These data suggest that women affected by CAIS are at an increased risk for osteoporosis despite exposure to endogenous or exogenous estrogen.[20] Several preparations for estrogen therapy are available, including the natural estrogen estradiol, which can be given orally or transdermally. Synthetic estrogens can be given in the form of the combined oral contraceptive pill. Some evidence supports the use of natural estrogens as transdermal hormone replacement therapy because this administration method might be more physiological than oral delivery. Since women with complete androgen insensitivity syndrome do not have a uterus, they can be treated with continuous, unopposed estrogen.[23] Upon follow-up two weeks after bilateral gonadectomy, patient was started on continuous 17β stradiol transdermal gel (0.75mg once a day) and calcium with vitamin D supplementation. DEXA scanning to examine bone mineral density should also be instituted in regular basis.

Following the diagnosis of CAIS, the gynecologist as the primary physician is left with a dilemma of whether to disclose the correct diagnosis to the patient or not. To explain the diagnosis by telling the patient that she is fundamentally male but with abnormal sexual development may be embryologically correct but may be devastating to the patient since such knowledge can destroy her identity. The psychological and social implications of disclosure of the diagnosis, gender assignment and fertility issues are very important and the gynecologist has to be sensitive to the impact of disclosure to the patient. The gynecologist should also be aware of and recognize the psychological problems that are often associated with the diagnosis. It's not enough that a patient is treated of her physical condition. The means by which a patient copes with and adapts to the diagnosis of CAIS (and for any DSD for that matter) is more important as this determines her future quality of life.

Initial disclosure done by the gynecologist concerning facts about karyotype, gonadal status, and prospects for future fertility requires a flexible individual based approach[10] and should be patient-centered.[42] Patient-centered care according to the Clinical Guidelines for the Management of Disorders of Sex Development in Childhood means remaining clearly focused on the well-being of individual patients. In the case of DSDs which includes CAIS, this specifically involves the following principles: 1) provide medical and surgical care when dealing with a complication that represents a real and present to the patient's physical well-being; 2) recognize that what is normal for one individual may not be what is normal for others; 3) minimize the potential for the patient and family to feel ashamed, stigmatized, or overly obsessed by genital appearance; 4) delay elective surgical and hormonal treatments until the patient can actively participate in decision-making about how his or her own body will look, feel and function; 5) respect parents by addressing their

concerns and distress emphatically, honestly and directly; 6) directly address the patient's psychosocial distress (if any) with the efforts of psychosocial professionals and peer support; and, 7) always tell the truth to the family and patient.[42] Disclosure should begin with explanation that the patient is female with an abnormal gonad, and it should build on that assumption.[10] Fortunately, the matter of gender assignment is not often difficult in people with CAIS since almost universally, CAIS patients are reared as girls as a combined result of their female external appearance at birth, diagnosis in later childhood or adolescence when testes are detected or primary amenorrhea is noted, and the overwhelming number of reports of gender identity for the vast majority of affected individuals.[43] Our patient has been reared and perceived as a female throughout her life.

The need for gonadectomy will ultimately require that the gonadal and chromosomal sex be explained, but care must be taken to do this in a way that does not disturb the overall gender identity.[10] Even if textbooks tell us that the presence of a Y chromosome in a person does not necessarily mean and should not be associated with "maleness," patients always do. Such knowledge of possessing the Y chromosome and testes can have a profound psychological impact in the sense of identity of the patient and can crush her self-confidence. This in turn can affect affect the quality of her interpersonal and intrapersonal relationships. The gynecologist should emphasize that more than the presence of the Y chromosome and testes, gender identity is dependent on sex of rearing and how others perceive her to be. After disclosure of her diagnosis, our patient admitted feelings of insecurity, inadequacy and doubt of her true gender identity. She confessed to having frequently asked her family, boyfriend and peers on their perception of her. In subsequent gynecologic visits, her female gender identity was reiterated. Counselling of her family was also done, highlighting their role in assuring the patient their perception of her as a female, and acceptance of her as a person no matter what her condition is.

In our country, having children is expected in any relationship and the capacity to bear children is often used as a gauge of womanhood. Women with no uterus and infertile couples with no chance of bearing children are in pain. Possessing a Y chromosome and testes, and being informed of her reproductive limitations, our patient has the potential of going into depression. A Danish study shows that suicidal thoughts and psychological and psychiatric counseling is more abundant among patients with disorders of sex development than in normal females.[43] Thus, supportive psychotherapy from the Psychiatry department was also provided to our patient.

Empowering CAIS patients by giving them the right knowledge about their condition including the treatment options that are available and the pros and cons associated with each could limit the risk of psychological problems. This is important for satisfactory development into adulthood. An excellent way to eliminate shame and secrecy is to provide patients with information about peer support groups so that they may communicate with others who share a common medical history. Examples of such groups include, but are not limited to, the dsdfamilies, AISDSD, the MAGIC Foundation, and CARES[43] and online AIS support groups such as aissg.or and aisdsd.org.[44, 45] We encouraged our patient to join an AIS support group and meet women with the same condition. This is in part, empowering our patient with the knowledge that she is not alone and thus, decreasing feelings of shame, insecurity, and humiliation so often associated with DSD.

People with DSDs desire the same things in life as everyone else – to find someone who will love them, to be valued as human beings, to feel at home in their own bodies, to be able to have satisfactory sexual relations should these be desired, to be able to trust their medical advisers and to be integrated in the whole community.[45] Knowing that our patient has a live-in partner with plans of future marriage and adoption, emphasis was made on her social role as a female. It is apparent that although she may not become pregnant, she can still be a normal-functioning female who is capable of giving and receiving affection, and can contribute much to society by being an inspiration to other individuals who may have the same DSD. From the time our patient joined the online AIS support, she has come across

several Filipinas who also have symptoms of DSD but are too ashamed and frightened to seek consult and management. This made us realize that there may only be a few reported cases of CAIS but this may not be reflective of the actual number of women having the condition since only a few seek medical attention. We have encouraged her to advise these "peers" to seek medical attention, so that they too, will not live in fear, insecurity and isolation for the rest of their lives.

Two months after the diagnosis of CAIS, the patient showed acceptance on the diagnosis of AIS, with positive outlook in life and with no signs of depression. Counselling, family support and supportive psychotherapy helped her cope with her condition. At the end of the day, what really enabled the patient to accept her condition is the understanding and realization that she is not alone … psychosocial support is available and that other women share the same medical history like hers. Research shows that obtaining support from and connecting with others with a similar diagnosis is the single most important step on a journey to emotional healing and empowerment.[46] We adhere to the idea that the manner in which patients are supported and educated about their condition, including provision of peer support and making them realize that they are not alone and that they are accepted as they are optimizes the quality of life for people with CAIS.

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