Female with Intersex Disorders of Sexual Development in a 23 year old: A Case Report

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Intersex disorder is a group of conditions where there is a discrepancy between the external and internal genitalia. The older term, hermaphroditism came from the Greek names of gods and goddess, Hermes and Aphrodite. But these days, it has been replaced as disorders of sexual development (DSD). A patient with an intersex disorder has sexual development which is influenced by different chromosomal, hormonal, genetic, gonadal, genital and psychological attributes. When these aspects are not in congruence with each other, it can create problems on the person's identity, personality, family and interpersonal relationship.
This case is a 46XX disorder of sexual development (formerly termed female pseudohermaphroditism), with 46XX karyotype and ambiguous genitalia noted at birth. The different aspects of management including its multidisciplinary approach will be discussed. This involves gynecologists, endocrinologists, urologists, pshychiatrists, surgeons and counsellors.

Key words: congenital adrenal hyperplasia, gender assignment

Introduction

In the consensus statement on management of intersex disorder, authored during the International Consensus Conference on Intersex Disorder, it has been proposed to use the term Disorder of Sexual Development (DSD) in replacement to older terms such as intersex, pseudohermaphroditism and sex reversal.[16] The new term encompasses all congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical.

The most common cause of this disorder is congenital hyperplasia, which is an autosomal recessive metabolic disorder caused by a defect in any of the 5 enzymes involved in cortisol synthesis. The most common of these is the 21-hydroxylase deficiency accounting for 95% of cases. Further divided in 3 categories salt wasters, patients with virilization aldosterone deficiency; simple virilizer, virilization without salt wasting; and non-classic, patient without virilization or salt wasting.[6]

Data on DSD are limited however, it is estimated that the overall incidence of DSD is one in 5,500. Congenital adrenal hyperplasia and mixed gonadal dysgenesis are the most common cause of ambiguous genitalia constituting approximately 50%.[22]

In 2006, The Lawson Wilkins Pediatric Endocrine Society and the European Society of Pediatric Endocrinology, on the concensus on the management of intersex disorders, presented a proposed nomenclature on classification of DSD, that must be understandable to patients and their families:

This is the new classification of DSD[23]

Sex chromosomal DSD

1. 45, X (Turner syndrome and variants)
2. 47, XXY (Klinefelter syndrome and variants)
3. 45, X/46, XY and variants
4. 46, XX/46, XY and variants

46, XY DSD

1. Gonadal (testicular) dysgenesis
   a. Complete gonadal dysgenesis (Swyer syndrome)
   b. Partial gonadal dysgenesis

c. Gonadal regression
d. Ovotesticular DSD

2. Disorder of androgen biosynthesis or action

a. Androgen biosynthesis defect (eg. 17-hydroxysteroid dehydrogenase deficiency; 5 alpha-reductase deficiency)
b. Defective androgen action (eg. complete androgen insensitivity syndrome [CAIS] and partial androgen insensitivity syndrome [PAIS])
c. LH receptor defect (eg. Leydig cell hypoplasia)
d. Disorder of anti-mullerian hormone and anti-mullerian hormone receptor (eg. persistent mullerian duct syndrome)

46, XX DSD

1. Disorder of Gonadal (ovarian) development
   a. Ovotesticular DSD
   b. Testicular DSD
   c. Gonadal dysgenesis

2. Androgen excess
   a. Fetal level (e.g. CAH)
   b. Feto-placental level (e.g. Aromatase deficiency)
   c. Maternal level (e.g. maternal ovarian or adrenal tumor)

The Case

This is the case of A.M., a 23 year old, raised as a female, single, Catholic, born in Zamboanga Del Sur and currently residing in Mabalacat, Pampanga.

Four years prior, A.M. consulted a private physician with a chief complaint of "having two sexual organs". The attending doctor requested an ultrasound, which revealed an infantile uterus but no ovaries were noted. Moreover, patient experienced "penile pain after a heterosexual act". No medications were taken. Patient sought consultation in a government hospital. He was advised further evaluation and was subsequently referred to our institution.

Patient has unremarkable past medical and family history.

According to her mother, ambiguity was first noted at birth but was medically documented by a pediatrician when the patient was brought to the hospital at eight months old due to upper respiratory tract infection. She was advised to have her work-ups but did not comply.

At three years old, the ambiguity became more obvious to her mother but due to financial constraint no consultation was done. In her teenage years, she had no menarche and was slowly developing male features (signs of virilization). She was now more attracted to females and eventually had two serious relationships with females, and currently with a girlfriend for more than three years. She is a high school graduate, non-smoker, non-alcoholic beverage drinker and has been working as a factory worker for three years. She is the youngest of five siblings.

On physical examination, the patient appeared phenotypically male, with short stature and hirsutism. Breast development was Tanner stage 1. Inspection of the external genitalia showed patient has Tanner stage 5 in pubic hair growth. There was presence of what looked like a "penis without a urethra", two mounds of soft tissue lateral and inferior to the "penis" that looks like the labia majora. The urethra is situated about 0.5 cm from the penile root. A vaginal introitus was present. On internal examination, the vagina was smooth, admitted 1 finger, 7cm in depth with a blind end, no cervix was appreciated. On bimanual examination, the uterus was not palpable nor any adnexal mass noted. (Figure 1)

Transvaginal ultrasound was done, revealing an infantile uterus and small ovaries (Figure 2a). CT scan revealed bilateral adrenal hyperplasia (Figure 2b). Karyotype was requested revealing a chromosomal make up of 46 XX (Figure 3).

Patient was referred to a urologist and underwent cystoscopy and genitogram, examination revealed small uterus, visualization of the underdeveloped vagina, cervical and endometrial cavities, including both fallopian tubes and with a short common urogenital channel, normal urethra which leads to a well-developed bladder (Figure 2c).

The clinical presentation together with the physical findings and diagnostic results lead us to believe that this is a case of 46XX disorders of sexual development secondary to congenital adrenal hyperplasia.

Discussion

The salient features of the case include a patient who currently looks like a male. At birth, she was noted to have an ambiguous genitalia. She was initially raised as a female. Later, she started getting virilised, and at puberty has assumed the role of a male. In a physical examination his or her genitalia seem to contain two sexual organs, the presence of uterus and ovaries on ultrasound, a 46 XX karyotype, adrenal hyperplasia on CT scan, elevated testosterone, progesterone, ACTH(Adrenocorticotropic hormone), DHEAS(Dehydroepiandrosterone sulphate), 17 Hydroxyprogesterone and normal cortisol.

The most common variant of ambiguous genitalia is the 46XX disorders of sexual development secondary to congenital adrenal hyperplasia. By definition, it is a genetic

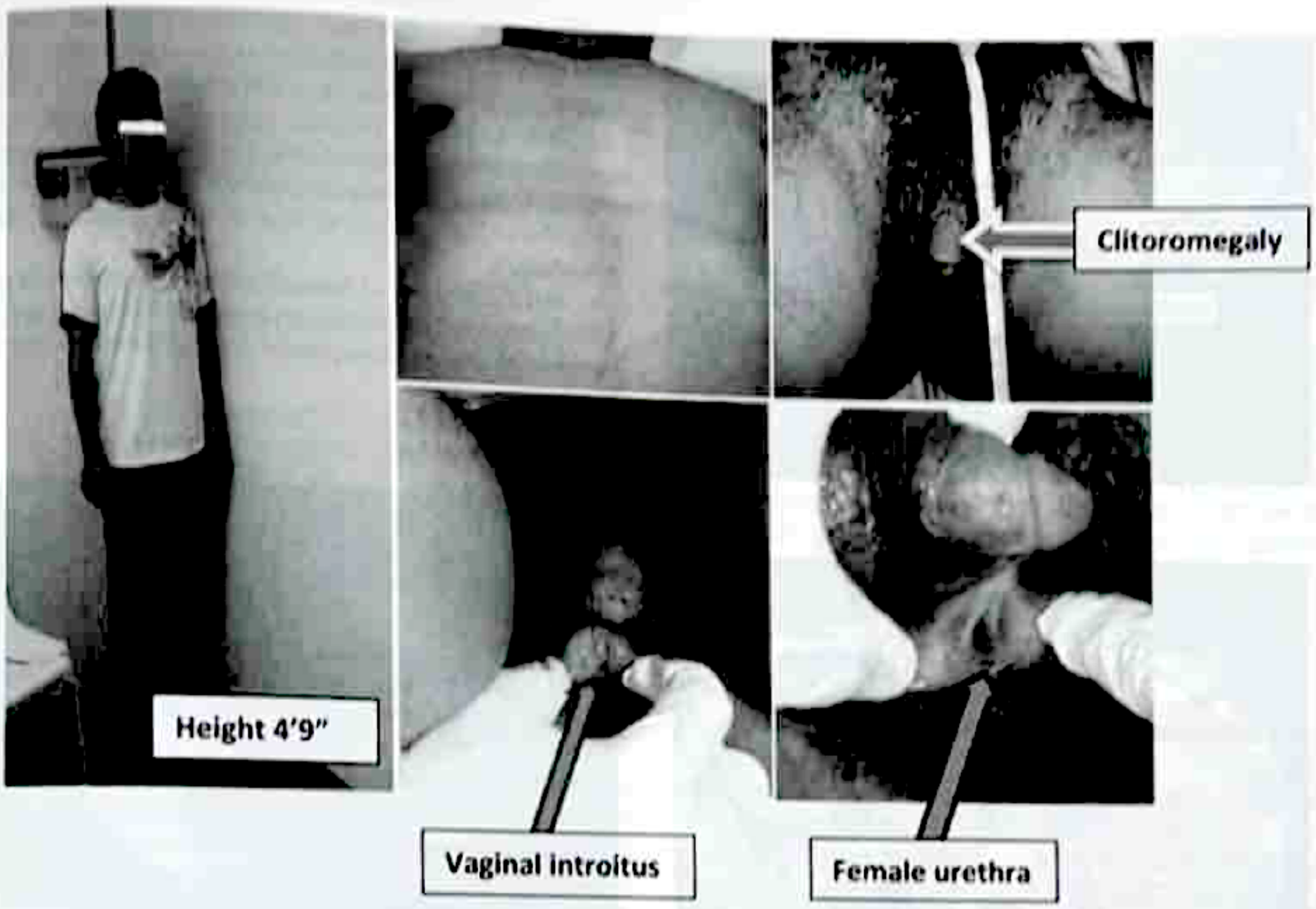

Figure 1. On physical examination, patient appears phenotypically male with short stature.

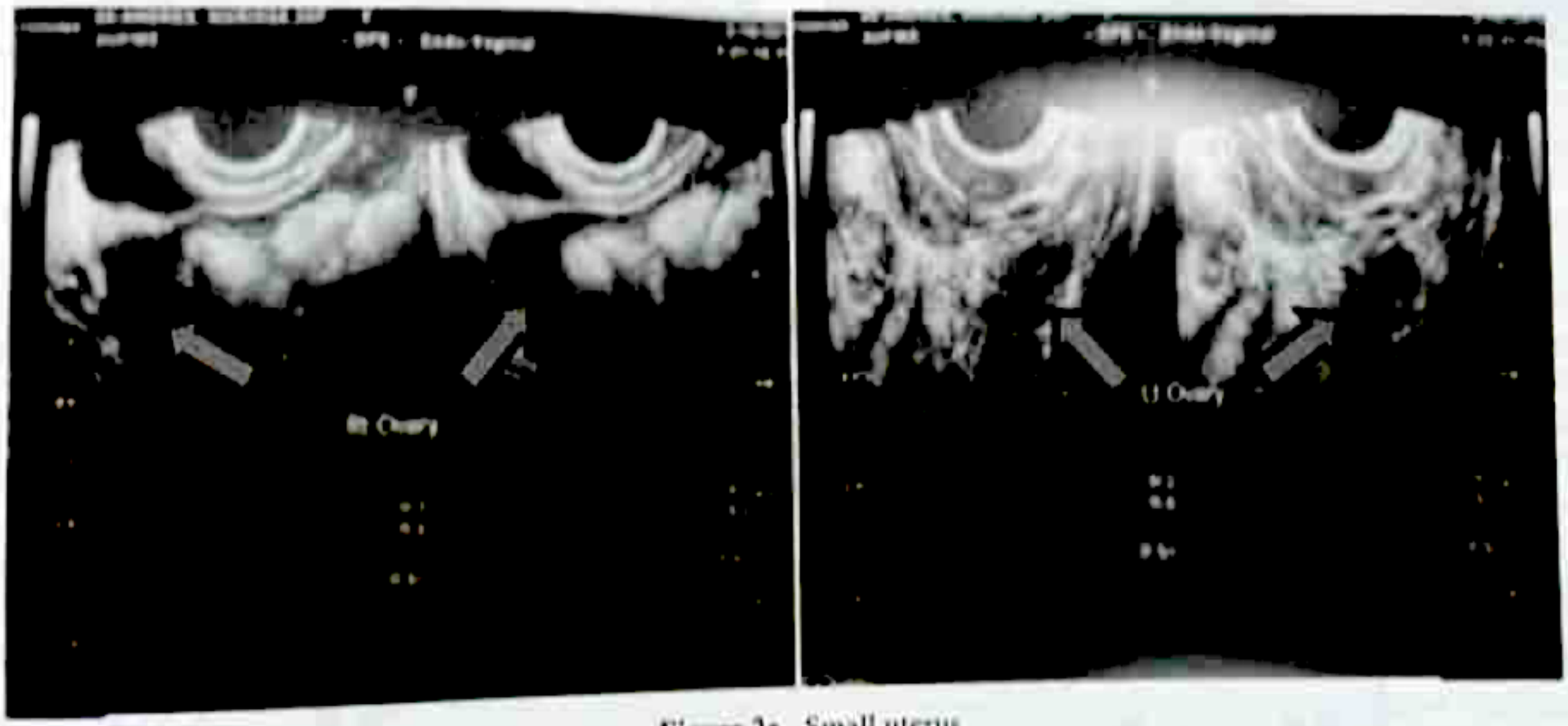

Figure 2a. Small uterus

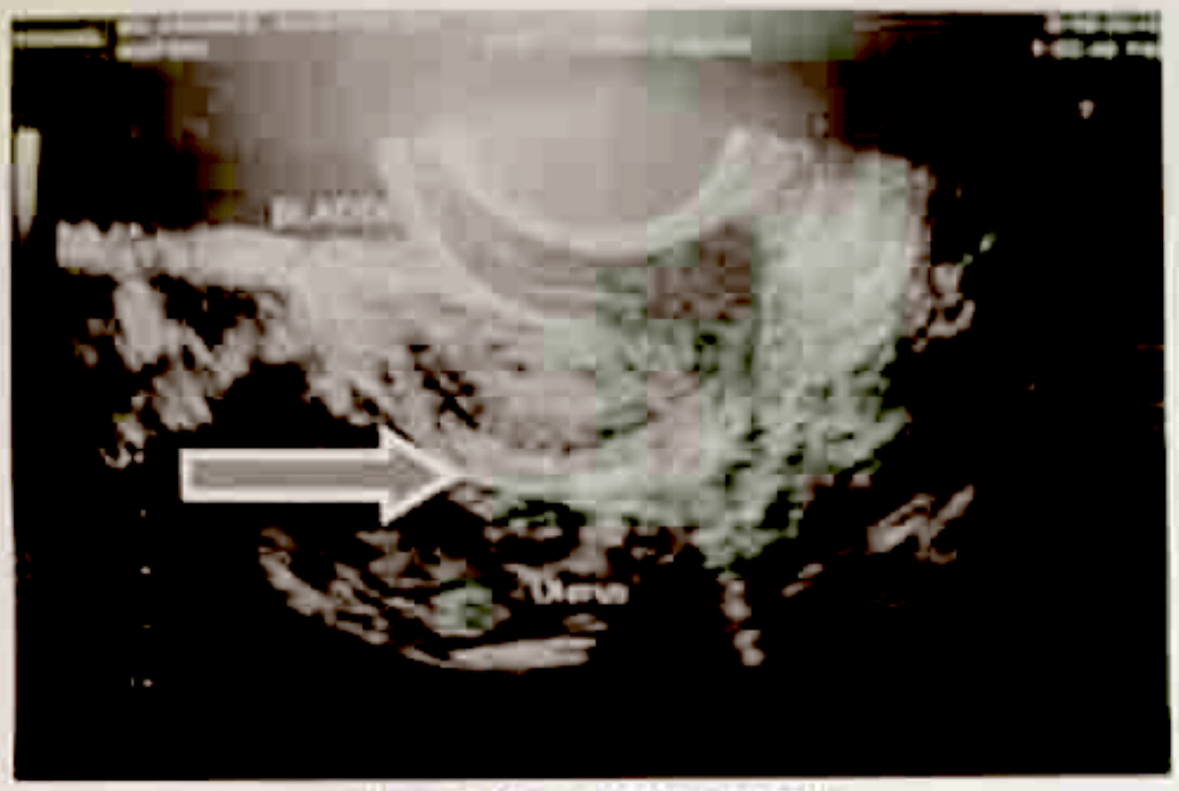

Figure 2b. Infantile uterus

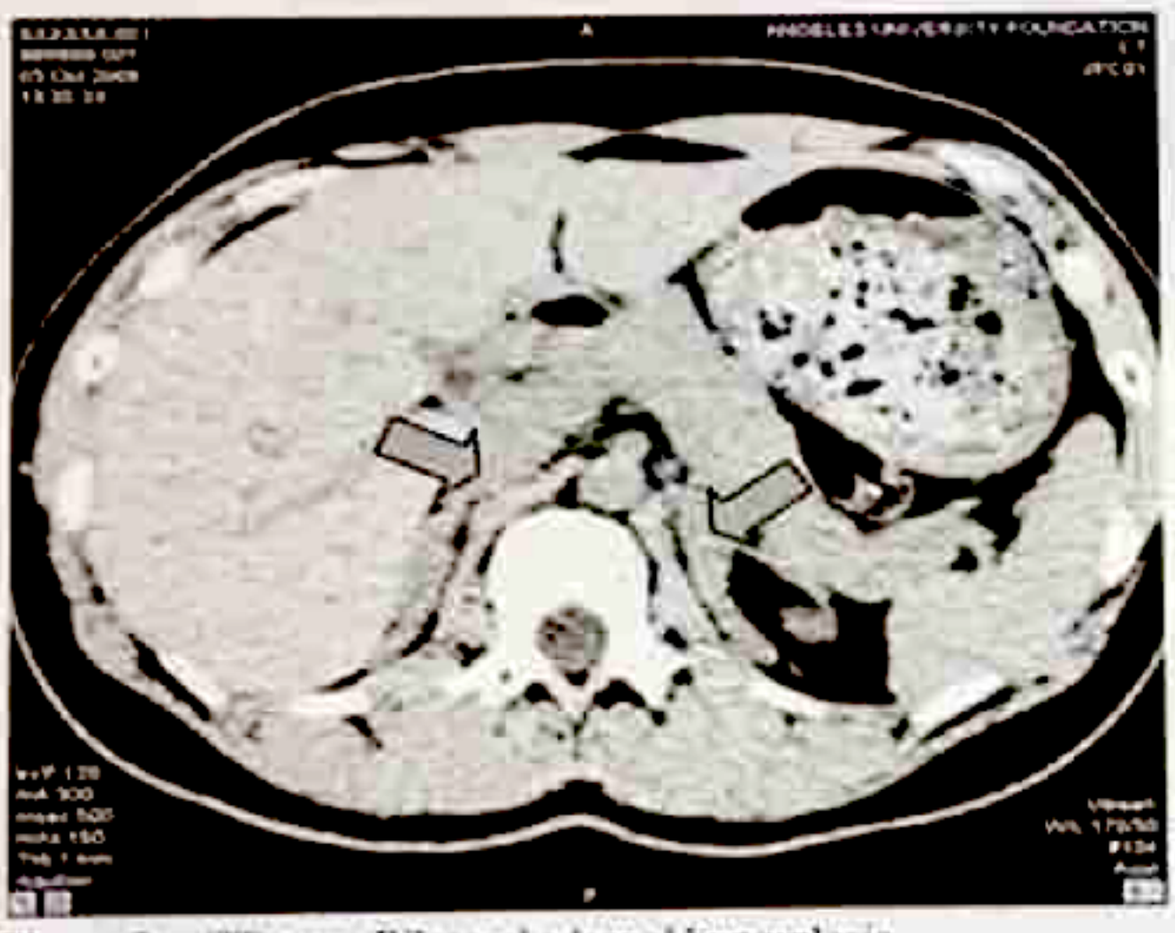

Figure 2c. CT scan-Bilateral adrenal hyperplasia.

female with ovaries and uterus but virilised external genitalia. The worldwide incidence of classic forms of CAH is approximately 1 in 15,000 with ethnic and racial variability. In the Filipino population, the newborn screening program reports an estimated crude incidence of classic CAH to be approximately 1 in 7,000 which is considered high compared to prevalence reports in most population.[1]

46XX disorders of sexual development by itself may arise from either endogenous production of androgens or exogenous androgen exposure such as from a maternal source.

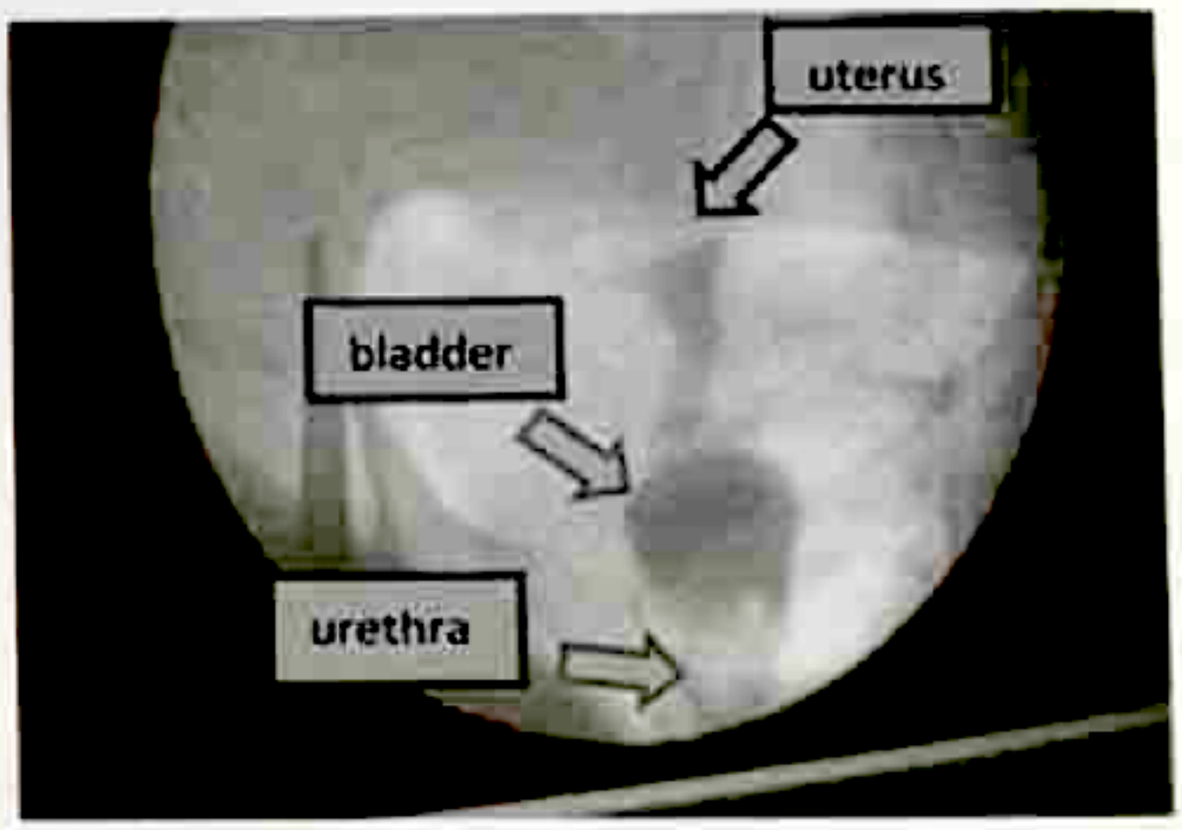

Figure 2d. Cystoscopy and genitogram-small uterus; underdeveloped vagina, cervical and endometrial cavities and both fallopian tubes. Short common passage urethra leading to a well-developed bladder.

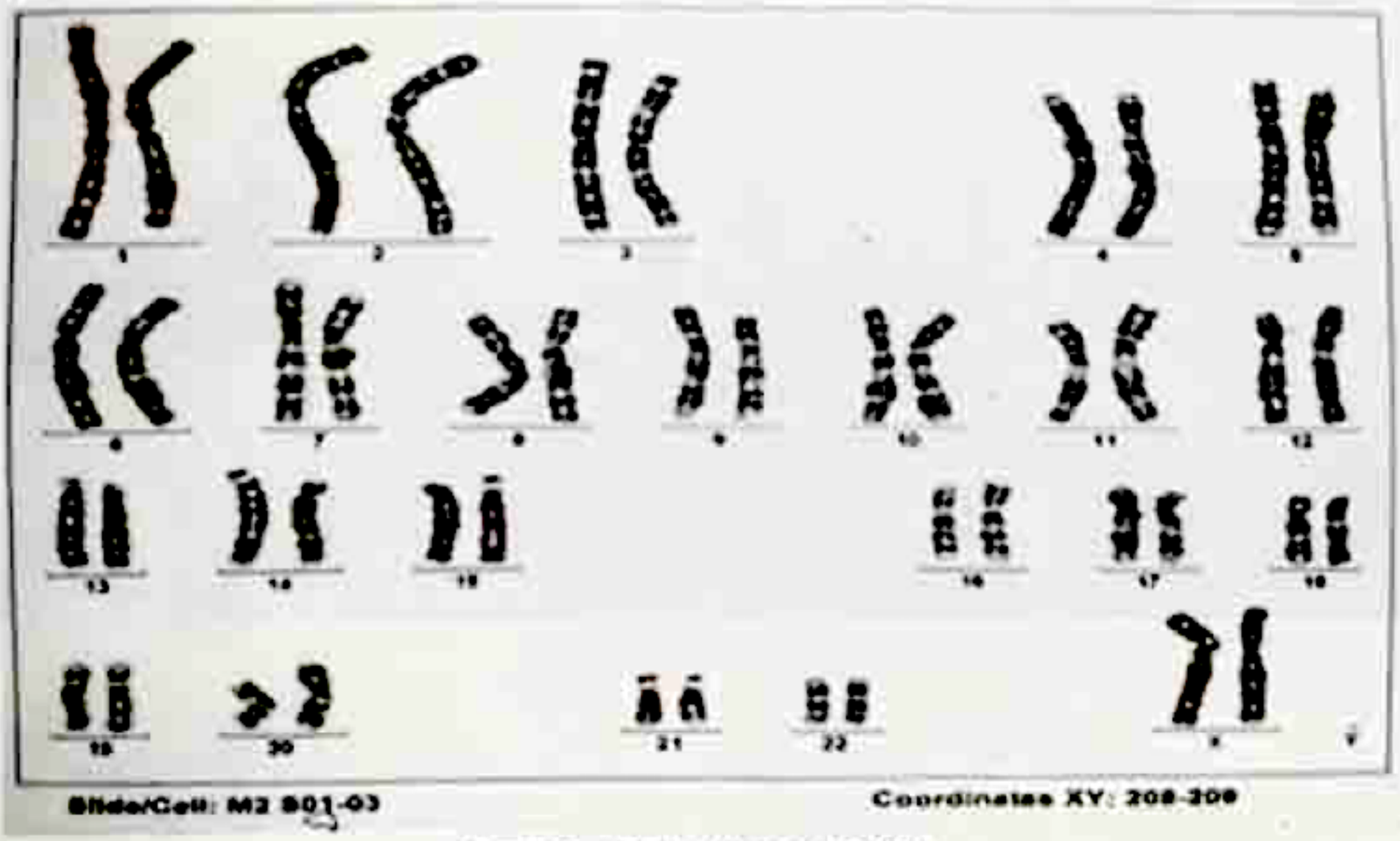

Figure 3. Karyotyping (46 XX)

Endogenous sources of excess androgens maybe from an adrenal hyperplasia or a tumor. The patient on CT scan was noted to have adrenal hyperplasia. Adrenal hyperplasia is an autosomal recessive disorder characterized by deficiency of one of the multiple enzymes involved in the adrenal synthesis of cortisol. It could be any of the following:

1. 21-Hydroxylase deficiency
2. 11B – hydroxylase deficiency
3. 3B-hydroxysteroid dehydrogenase deficiency

The most common is the 21 – hydroxylase deficiency accounting for about 95% of cases. There are three clinical forms based on severity; salt wasting, simple virilising and the non-classical form. [2]

The salt wasting form is characterized by 46XX disorders of sexual development at birth together with salt wasting. The latter can cause significant loss of sodium and water causing dehydration and can be potentially life threatening.

About 25% produces enough aldosterone and clinical manifestations are limited to virilization.

The non-classical form does not have ambiguous genitalia but produces signs of virilization during puberty.

The patient has ambiguous genitalia since birth and does not manifest with salt wasting disease; hence is more fitted to be classified to have a simple virilising form.

The male and female internal reproductive organs develop from the Wollfian and Mullerian ducts respectively. Beyond the 8th week of gestation, one of the ducts starts to differentiate and the other one regresses. Since the patient has a karyotype of 46XX, she doesn't have a Y chromosome that will dictate the formation of testes which in turn will produce the anti-mullerian hormone and testosterone; the latter causes the mullerian duct to regress and the wollfian duct to differentiate. The absence of the anti-mullerian hormone and testosterone in the patient has caused her internal reproductive system to develop into a uterus, ovaries and fallopian tubes as evidenced by her ultrasound findings. At 10th week age of gestation, the development of the internal reproductive organs is completed. [3]

It is only at 10-12 week age of gestation that the adrenal cortex reaches a level of significant function; during this time, an increase in androgen levels will no longer modify the internal reproductive organs. However, the external genitalia continue to develop until the 20th week of gestation, hence an increase in the androgen level will modify its development. [4]

Depending on the time of onset, quantity available and duration of exposure, the presence of androgen is manifested by varying degrees of fusion of labioscrotal folds, clitoral enlargement (the degree of which is more dependent on the quantity of androgen rather than the timing of excess), and anatomic changes of the urethra and the vagina. This is manifested in our patient by the presence of clitoral enlargement (which she mistook for a penis), the absence of labia minora, the presence of labia majora with wrinkled skin, a urethra that is situated immediately inferior to the enlarged clitoris ("hypospadia-like") and a vaginal canal.

A useful approach to a person with ambiguous genitalia would be to delineate the presence or absence of congenital anomalies. Karyotyping is mandatory in all cases. A determination of 17-OH progesterone levels, if elevated, leads to the diagnosis of congenital adrenal hyperplasia or multiple defects in testosterone biosynthesis. When levels of 17-OH progesterone levels are normal, maternal androgen-secreting tumors need to be ruled out. In adults, 17-OH progesterone must be measured first thing in the morning to avoid later elevations due to the diurnal pattern of ACTH secretion. The baseline 17-OH progesterone should be less than 200ng/L.

The patient's blood examination showed the presence of elevated 17- hydroxyprogesterone, DHEA-S, testosterone and progesterone. In the synthesis of cortisol and aldosterone from cholesterol, 17-hydroxyprogesterone is a substrate for 21-hydroxylase enzyme in the production of deoxycortisol. In the absence of the enzyme, it accumulates and the pathway is shifted to the formation of androstenedione and testosterone. This explains the elevated levels in our patient.

In the simple virilising form of congenital adrenal hyperplasia, the enzyme deficiency is partial hence the patient produce cortisol and aldosterone, the level of which is compensated by the increased in ACTH. This is documented in the patient by the elevated ACTH and a normal cortisol level.

If the patient's condition was detected at birth (new born screening), the patient should be monitored (electrolytes and glucose,) and started on steroids like hydrocortisone or fluorocortisone acetate; the former being the drug of choice. During pubertal stage, psychological counselling which provides the discussion on the medical situation of the person is conducted by someone who is knowledgeable about their conditions. Areas that are of particular concern to some CAH patient includes lifelong requirement for medication, genital surgery and sexuality.

In an untreated female with adrenal hyperplasia, patient will develop signs of progressive virilization. Pubic hair will appear, axillary hair then body hair and beard. Bone age is advanced because of early epiphyseal closure, shortened stature in adulthood. Progressive masculization continues with the development of the male

habitus, acne deepened voice and primary amenorrhea and infertility as seen with the patient.

For this case, a multi-disciplinary approach was done. The patient was referred to an endocrinologist, a urologist, a psychologist and a chaplain. They have provided all the medical information that brought about his condition, genital appearance and therapeutic options and their possible consequences.

It turned out that the patient's main concern is about gender assignment. The patient, despite her being genetically female, certainly wanted to live life as a male.

Gender assignment should be made after a thorough diagnostic evaluation. Influencing factors include diagnosis, genital appearance, therapeutic options, fertility potentials, cultural practices and pressures and parental views. Traditionally, gender assignment is based on the optimal gender policy by Hampson and Money in 1956. The latter recommend that the clinical decision should be made before the age of 2. However, clinical experiences proved that not all patients who had been assigned to either sex during their childhood are satisfied later in life, hence current trends have shifted to the full consent policy which involves delay of surgery and when the patient is in later stages of gender development, all medical information is provided to the patient and his parents and their full participation in the decision making is fully encouraged.[9] It has 3 important stages, the first stage, gender identity, is the recognition of one's self as male or female. The second stage, gender role, refers to the social behaviour corresponding to society's expectations for a given gender. The third stage, sexual orientation, is a person's erotic interest in male or female sexual partner.[9]

Because she has chosen to be a male, no medical or hormonal treatment was needed. The patient underwent a series of psychological and spiritual counselling with our hospital chaplain and psychiatrist concerning his or her gender preference and the result of the karyotyping which is 46 XX.

Patient was seen by a urologist for the assessment of the urethra and penile straightening, results of which will permanently change his life. The patient was provided with full disclosure of the effects of the surgical intervention both anatomically and functionally. Furthermore, patient was made aware of all the clinical information regarding limitations of the surgery and the inability to procreate. The patient independently and whole-heartedly decided to proceed with the operation and be a man. Though only half a man he could be, small things like going to comfort rooms of males without having to sit on the toilet bowl, or entering a female comfort room without being suspected maliciously is worth more than enough to be at least accepted socially as a male.

After 2 years of thorough counselling and working with the different caregivers of the multidisciplinary team, the patient agreed to have the surgery done. The patient underwent metoidioplasty, the release of chordee (penile straightening) and translocation of preputial skin from the dorsum to ventral aspect around the urethral plate, the first step in the correction of the urethra(Figure 4).

Pre-Op

Release of chordee

Post OP

Figure 4. First Stage: Metoidioplasty, release of chordee (penile straightening) and translocation of preputial skin from the dorsum to ventral aspect around the urethral plate.

Ten months later, the second part of the correction of the urethra was done, the patient underwent colpocleisis or complete obliteration of the vaginal vault and urethroplasty, wherein the prepared preputial skin which was translocated around the urethral plate, was tubularized and anastamosed with the native urethra. Suprapubic cystostomy was also done. (Figure 5).

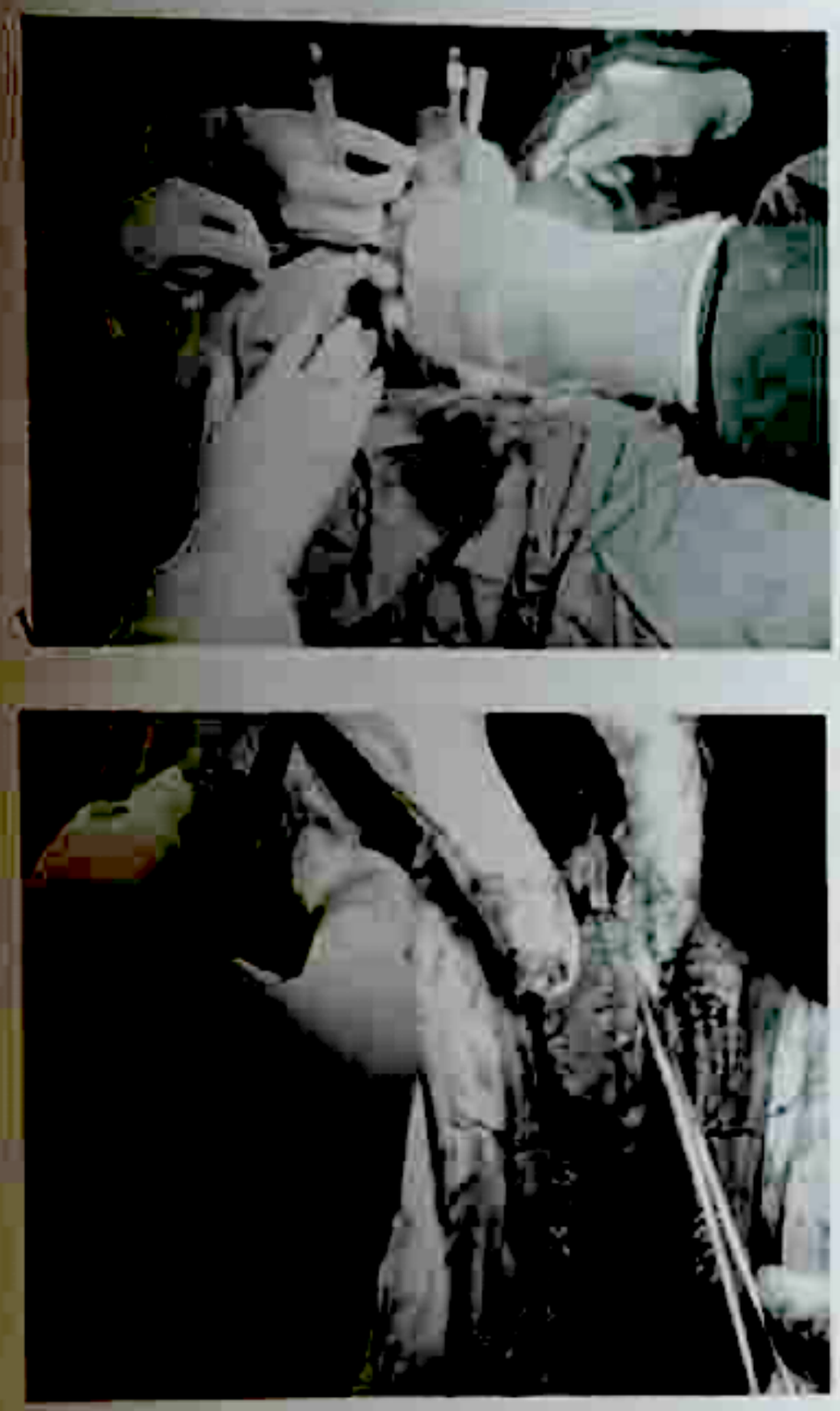

Figure 5. Second stage : Suprapubic cystostomy / urethroplasty / colpocleisis

After the two-staged surgery, the patient was able to achieve a total phallus length of 2.5 inches (6.35 cms) and the urethral opening was relocated near the tip of the ventral phallus. Most patients have satisfactory sexual performance as long as they present a penis size of at least 6 cm[22]. Five months after the surgery, on one of his follow up sessions, patient reported full functionality of phallus and disappearance of pains and expressed satisfaction with the over-all results.

Conclusion

Medicine, like all sciences, exhausts all means to find answers but cannot deliver them all.

We, as doctors, can present and undertake treatments but our jurisdictions may be limited by autonomy of the patient wherein he must decide which sexual orientation he or she prefers. Regardless of how much his or her genetic make-up may seemingly dictate, the answer can only be provided by the adult patient.

Ambiguous genitalia is usually not life threatening but can create social problems for the child and the family. Our patient has reached adulthood without any medical help nor supervision but still, though late, it may signify a desire to know and understand her/his condition and is seeking help.

For this reason a team of experienced specialists, including gynecologists, endocrinologists, psychiatrists and urologists as well as a spiritual counsellor were involved in this case.

In conclusion, we have been presented a case of CAH. The patient's medical condition was highlighted during his adult life when he became very concerned about his anatomic ambiguities. Despite the fact that the patient is

genetically female, the patient has slowly transformed into a male, physically and psychologically. He opted to assume a male role in a romantic relationship. The patient is the product of his parents love for each other and now, how he chooses to live and love, who he wants to be and who to love is his own decision and no one else's. This new person is the product of multidisciplinary team who love to provide the best care to patients based not on their beliefs but on the patient's best interest.

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