Diagnosis by Serendipity: A Case of Mosaic Turner Syndrome and Late Onset Congenital Adrenal Hyperplasia

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Congenital Adrenal Hyperplasia and Turner Syndrome are not very rare diseases. However, their combination may be confounding. Presented here is a case of a 54 year old nulligravid, with primary amenorrhea, short stature, absent breast development, hirsutism, signs of virilization, and clitoromegaly who came in due to hypogastric pain and an enlarging palpable hypogastric mass. Diagnostic procedures and surgical management are discussed.

Key words: Congenital Adrenal Hyperplasia, Primary Amenorrhea, Turner Syndrome

Introduction

Amenorrhea is defined as the absence of menstruation which may be primary or secondary.[1] Primary amenorrhea is the failure to reach menarche, and its incidence is about 0.1%.[1] Evaluation is warranted if there are no secondary sex characteristics by 13 years of age, and if menarche has not occurred by five years after breast development.[2] Secondary amenorrhea, on the other hand, is defined as the absence of menses for a period of time, usually longer than 6 to 12 months, in a previously menstruating patient.[3] The incidence of secondary amenorrhea is said to be 0.7 - 3.0%.[1] There is no published incidence of amenorrhea in the Philippines.

Various etiologies of primary amenorrhea may include outflow tract obstructions, gonadal dysgenesis, abnormalities of the central nervous system, various endocrine diseases, psychologic problems, and constitutional delay of puberty. Patients presenting with primary amenorrhea and short stature, should prompt the clinician to rule out a syndromic disorder such as Turner Syndrome. However, primary amenorrhea in the presence of virilization or sexual ambiguity may point to enzymatic causes such as Congenital Adrenal Hyperplasia. Both Turner Syndrome and Congenital Adrenal Hyperplasia are not very rare diseases. However, their combination may be confounding and may pose a great trouble in diagnosis.

This paper shall discuss an interesting case of a patient diagnosed with both Turner Syndrome and Congenital Adrenal Hyperplasia, the comprehensive diagnostic procedures done, and the treatment administered.

The Case

The index patient is a 54 year old single nulligravid, Filipino from Malabon City, who came in with a chief complaint of hypogastric pain. Patient was born, identified, and was raised as a female. Patient had female features at birth and claimed to have normal height and weight for age during her childhood.

At 13 years old, patient noted to have breast budding and development of pubic hair. At this time, patient also noted sudden rapid growth. At 16 years old, patient was noted to have clitoral enlargement with appearance of other masculine features such as hair on the upper lip and chin, deepening of the voice, increased muscle mass, and receding hairline. Patient

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claimed to have no history of exogenous hormones intake. No onset of menarche was noted. Patient did not seek any consult. Interval history showed still no onset of menarche, but still no consult was done. No medications were taken during this time.

One year prior to consult, patient noted hypogastric pain with a pain score of 7- 8/10, radiating to the lumbar area. This was associated with a gradually enlarging palpable non-tender hypogastric mass, approximately the size of a fist. This was not associated with any urinary nor bowel symptoms. Still, no consult was done and no medications were taken.

One month prior to consult, patient sought consult with a rheumatologist due to tingling sensation, numbness, weakness, and prickling pain over her thumb, index, and middle fingers on bilateral hands. Patient was diagnosed with carpal tunnel syndrome, advised immobilization and prescribed with unrecalled steroids. During the consult, the physician noted prominence of male features and upon further history, elicited a history of primary amenorrhea and a history of hypogastric pain with enlarging palpable hypogastric mass. Patient was then referred to a gynecologist.

Patient was a non-smoker and a non-alcoholic beverage drinker. Her past medical history was unremarkable, with no known comorbidities aside from her carpal tunnel syndrome, and no known allergies to food nor medications. Patient had no previous hospitalizations nor previous surgeries.

Patient was born from a non-consanguineous marriage, following a full-term pregnancy, at maternal age of 28. There were no known maternal comorbidities at the time of pregnancy and was eventually delivered via spontaneous vaginal delivery attended by a hilot, with no feto-maternal complications noted. No newborn screening was done. Patient was the fourth among seven siblings, with three males and four females. Growing up, she was said to be tomboyish, preferring boy's clothes, games, and activities. Due to the development of male appearance, patient conformed to a male gender identity and role, and was attracted to females. She had a relationship with another female who is now her live-in partner. Patient previously worked as a garbage collector for seven years. She then opened her own grocery store, selling commercial goods for 21 years. Further history revealed that she had never had her menarche, had no previous sexual contact, and is a nulligravid.

At the time of consultation, patient was conscious, coherent, ambulatory, not in cardiorespiratory distress with stable vital signs. Patient exhibited a short stature standing at 147 centimeters, weighing at 58 kilograms. Patient was classified as obese with a BMI of 27. Patient's external body habitus was that of a male phenotype with no apparent cushingoid features. There was receding hairline, and mild hirsutism with Ferriman- Galleway score of 9/36 (upper lip: 1; chin: 1; chest: 0; arm: 1; upper abdomen: 1; lower abdomen: 4; inner thigh: 1; upper back: 0; lower back: 0). On examination of the upper torso, there was webbing of the neck, and broad chest with widely spaced nipples. Breast development was that of Tanner's Stage III (Figure 1). The abdomen was noted to be globular with a palpable firm, movable, nontender 20 cm x 10 cm hypogastric mass. On genital examination, pubic hair was Tanner's Stage IV (Figure 2). Clitoris was noted to be 6 cm in length and 2.5 cm in width, signifying clitoromegaly (Figure 3). Vagina was 5 centimeters in length (Figure 4), with no cervix palpated. No inguinal mass palpated. Rectal examination revealed smooth tight sphincteric tone, with a globular, firm, movable, nontender mass, enlarged to around 20 weeks size, palpated at the hypogastric area. No blood nor fecal matter noted on examining finger. No edema noted on all extremities. No neurologic deficits noted.

Investigations

A whole abdominal ultrasound showed an enlarged uterus with inhomogenous parenchyma and multiple myomas. Transrectal ultrasound showed an infantile uterus with a mass described probably a subserous myoma, measuring 14.6cm x 7.2 cm x 14.8cm (Figure 5).

Laboratory examination was done which revealed the following significant results: FSH was decreased at 4.58 mIU/ml (NV 5-20 IU/ml); LH decreased at 0.48 IU/L (NV 5-25 IU/L); Testosterone was elevated at 4.7 ng/ml (NV: 0.1-0.75 ng/ml); 17- hydroxyprogesterone elevated at 77.96 ng/mL and 79.66 ng/mL 1-hour post-stimulation (NV: 0.19-0.71). Estradiol, progesterone, cortisol, DHEAS, CA-125, Beta HCG, thyroid function

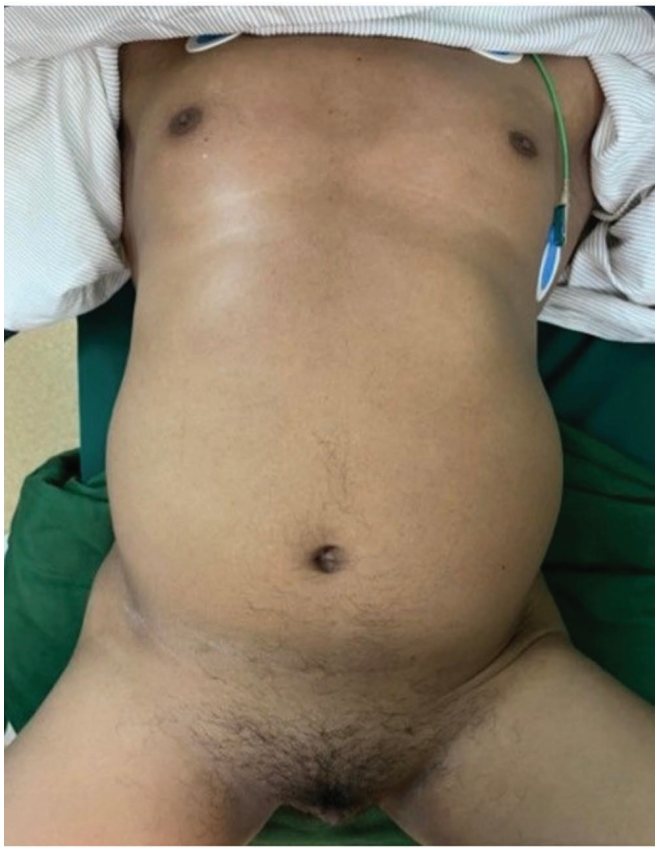

Figure 1. Breast development was Tanner's Stage III. The abdomen was globular with a palpable firm, movable, nontender 20cm x 10cm hypogastric mass.

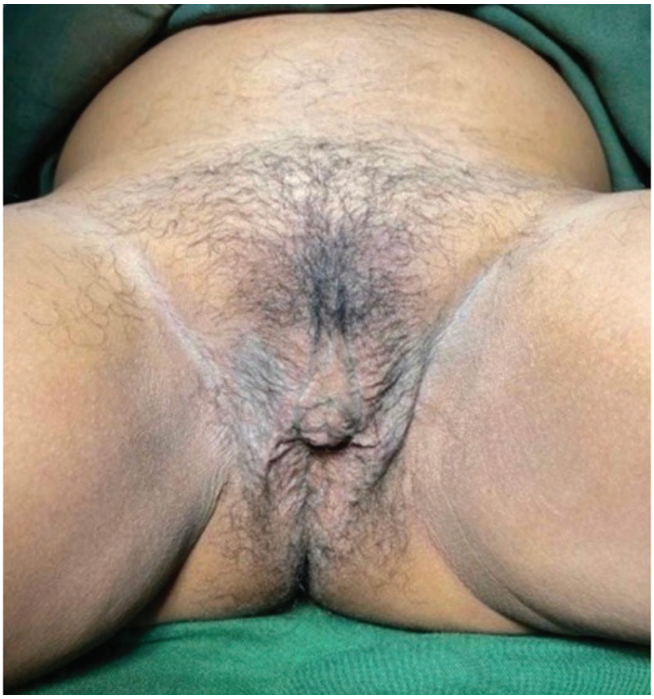

Figure 2. Pubic hair was Tanner's Stage IV.

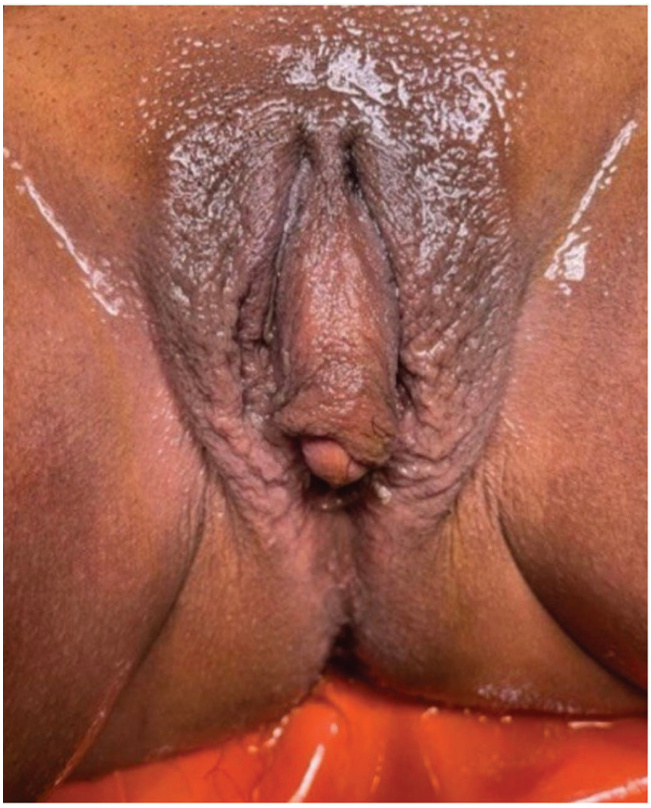

Figure 3. Clitoris was noted to be 6 cm in length and 2.5 cm in width, signifying clitoromegaly.

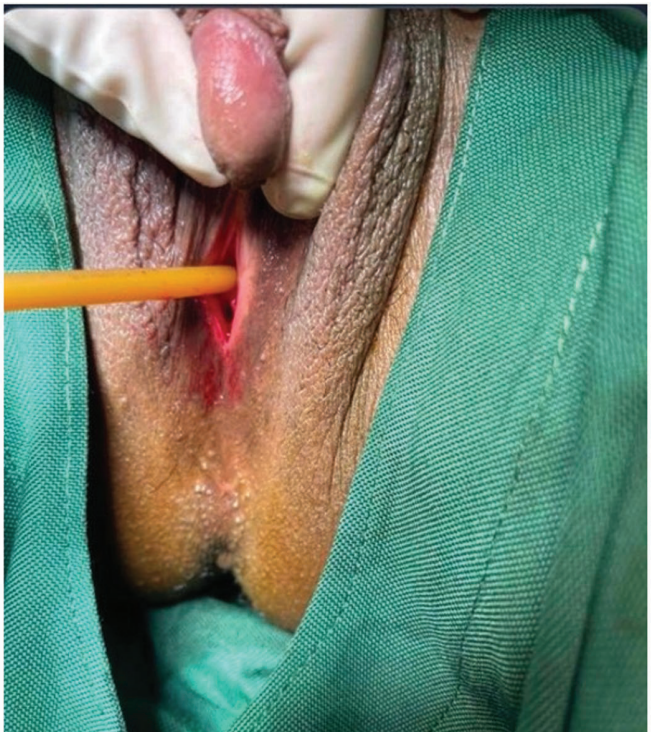

Figure 4. Vagina was 5 cm in length, with no cervix palpated.

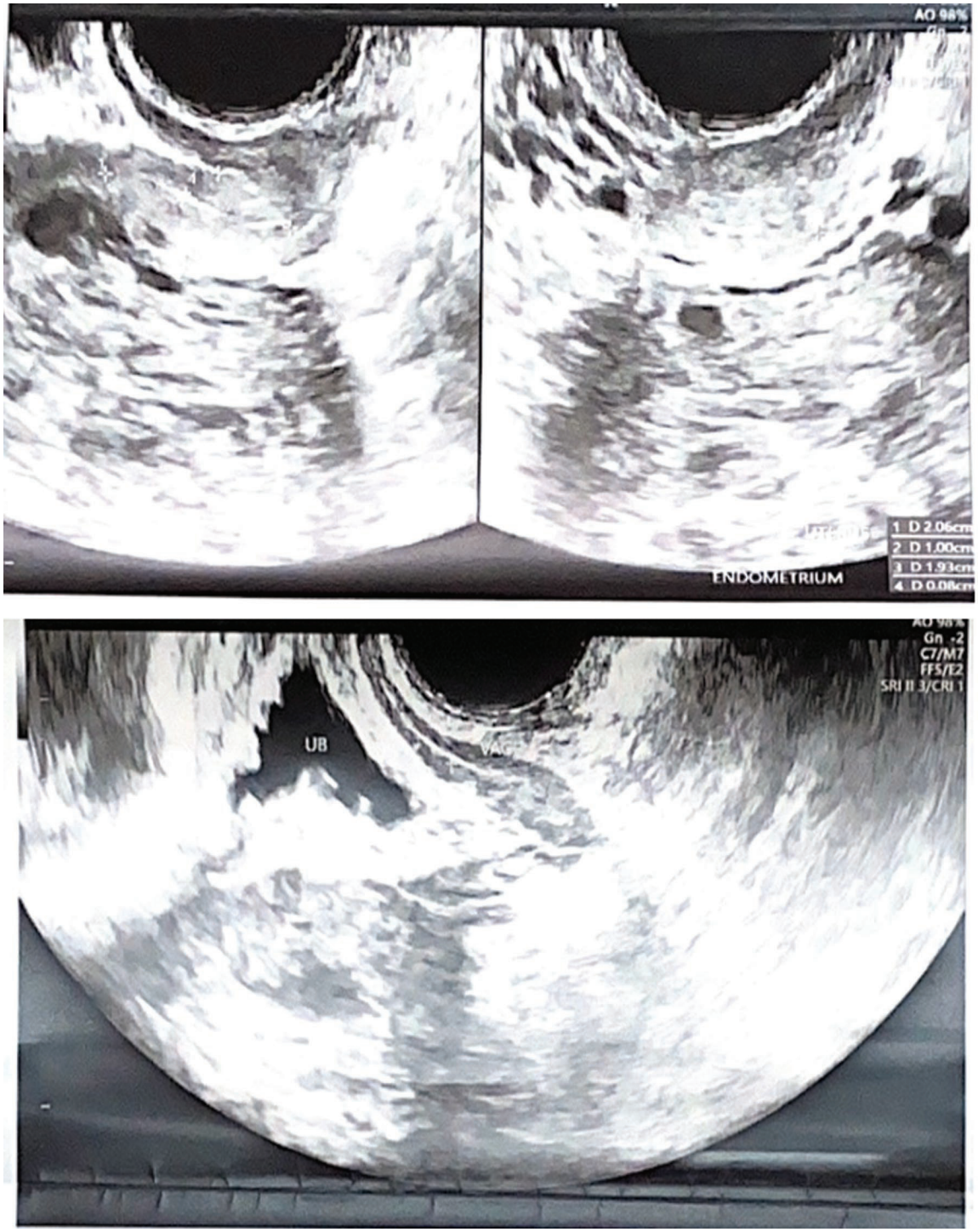

Figure 5. Transrectal ultrasound showed an infantile uterus with a mass described probably a subserous myoma, measuring 14.6cm x 7.2 cm x 14.8 cm.

test, cholesterol panel were all normal (Table 1). Patient's karyotyping showed: 45,X(2)/46,XX(48) Mosaic 45,X/46, XX with less than 10% 45,X cells in an adult (Figure 6). Patient underwent diagnostic hysteroscopy which showed a blind ending vaginal pouch with no cervix (Figure 7).

Table 1. Laboratory work-up low FSH and LH levels and high testosterone and 17- hydroxyprogesterone levels. Estradiol, progesterone, cortisol, DHEAS, CA-125, Beta HCG, thyroid function test, cholesterol panel were all normal.

	Result	**Reference Value**
FSH	4.58 mIU/mL	Follicular phase: 3.03 - 8.08 mIU/mL Mid cycle peak: 2.55 - 16.69 mIU/mI Luteal phase: 1.38 - 5.47 mIU/mI Post menopausal: 26.72 - 133.41 mIU/mL
LH	0.48 mIU/mL	Follicular phase: 1.80 - 11.78 mIU/mL Mid cycle peak: 7.59 - 89.08 mIU/mI Luteal phase: 0.56 - 14.0 mIU/mI Post menopausal: 5.16 - 61.99 mIU/mL
Estradiol	66 pg/mL	Follicular phase: 23 - 139 pg/mL Peri-ovulatory: 95-433 =pg/mL Luteal phase: 32 - 328 pg/mL Post menopausal: 0 - 33 pg/mL
Progesterone	14.47 ng/mL	Males: 0.28 - 1.22 Follicular phase: Non detectable - 1.40 ng/mL Mid Luteal phase: 4.44 - 28.03 ng/mL Luteal phase: 3.34 - 25.56 ng/mL Post menopausal: Non detectable - 0.73 ng/mL
Testosterone	4.7 ng/ml	0.1 - 0.75 ng/mL

Cortisol	Baseline: 304.48 nmol/L 1 hour post-stimulation: 441.08 nmol/L	138 - 690 nmol/L 138 - 690 nmol/L
17-OHP	Baseline: 77.96 ng/mL 1 hour post-stimulation 79.66 ng/mL	0.19 - 0.71 ng/mL 0.19 - 0.71 ng/mL
ACTH	219 pg/mL	< 46 pg/mL
DHEAS	5.15 umol/L	0.5-8.9 umol/L
TSH FT3 FT4	1.51 uIU/mL 5.57 pmol/L 14.42 pmol/L	0.34 - 5.6 uIU/mL 3.8 - 6.0 pmol/L 7.9 - 14.4 pmol/L
Total cholesterol Triglycerides HDL LDL VLDL HDL ratio	4.91 mmol/L 1.85 mmol/L 1.24 mmol/L 2.83 mmol/L 0.84 mmol/L 3.96	3.89 - 6.00 mmol/L up to 1.70 mmol/L 0.78 - 1.95 mmol/L 1.56 - 4.55 mmol/L 0.00 - 1.04 mmol/L
CA125 AFP	6.96 U/mL 2.31 ng/mL	0 - 35 U/mL 0 – 7
BHCG	<5	0 - 5.0 mIU/mL
Karyotyping	Karyotyping showed: 45,X(2)/ 46,XX(48) Mosaic 45,X/46, XX with less than 10% 45,X cells in an adult.	

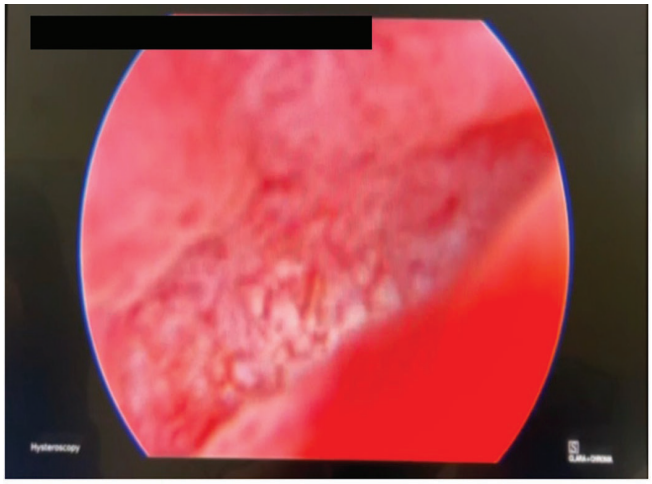

Figure 6. Blind ending vaginal pouch on diagnostic hysteroscopy

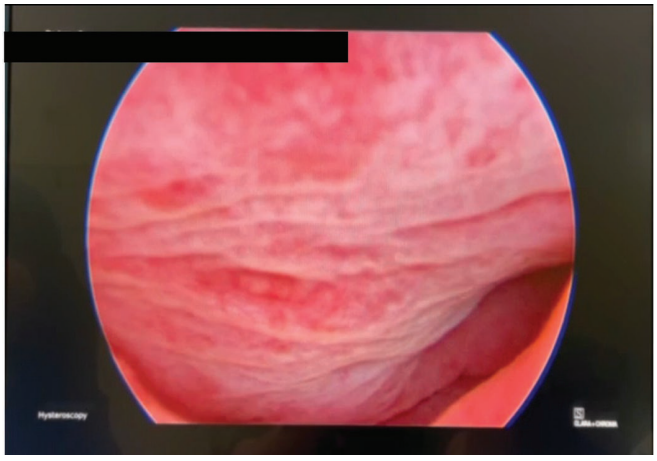

Figure 7. Panoramic view of blind ending vaginal pouch on diagnostic hysteroscopy.

Treatment

Patient then underwent exploratory laparotomy. Upon opening, there was no ascites. The uterus was globularly enlarged with pinkish tan smooth serosal surface measuring 12.0cm x 14.0cm x 8.0cm (Figure 8) . The cervix was absent. The right and left ovaries measured 2.1cm x 0.9cm x 0.5cm (Figure 9) and 2.5cm x 0.8cm x 0.4cm (Figure 10), respectively. The right and left fallopian tubes were 9.0cm x 0.5cm x 0.5cm and 7.0cm x0.5cm x 0.5cm long, respectively. On cut section, a solitary ovoid, well-demarcated, solid, firm, whorled-like myomatous submucous with intramural component mass measuring 10.2cm x 8.5cm x 8.0cm was noted which occupies the mid-posterior uterine corpus (Figure 11). Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy under general endotracheal anesthesia. Histopathology of the specimen showed leiomyomata uteri: submucous with intramural component measuring 10.2cm x 8.5cm x 8.0cm; intramural, multiple measuring 0.6cm to 1.2cm in diameter; atrophic endometrium; no diagnostic abnormality recognized, right and left ovaries and fallopian tubes.

Patient tolerated the procedure well with minimal blood loss. On first post-operative day, patient was stable with minimal post-operative pain. Diet was progressed and post- operative antibiotics and pain

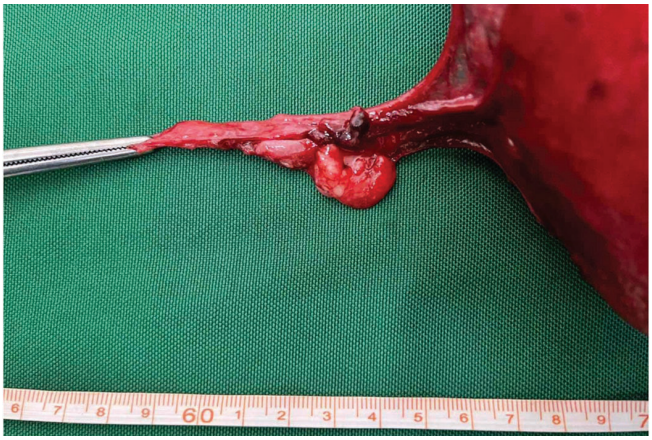

Figure 9. Gross image of right ovary.

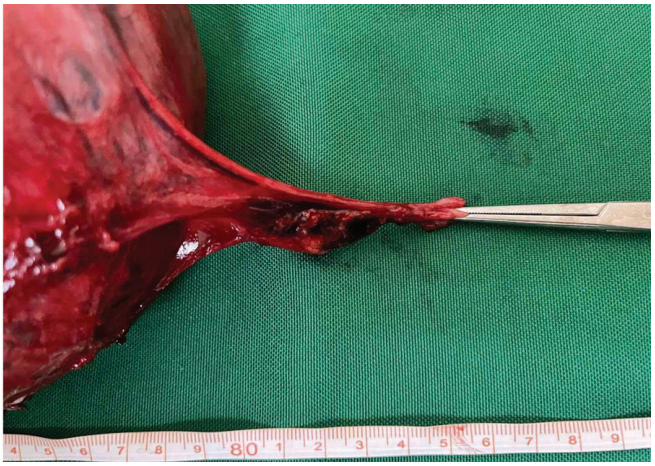

Figure 10. Gross image of left ovary.

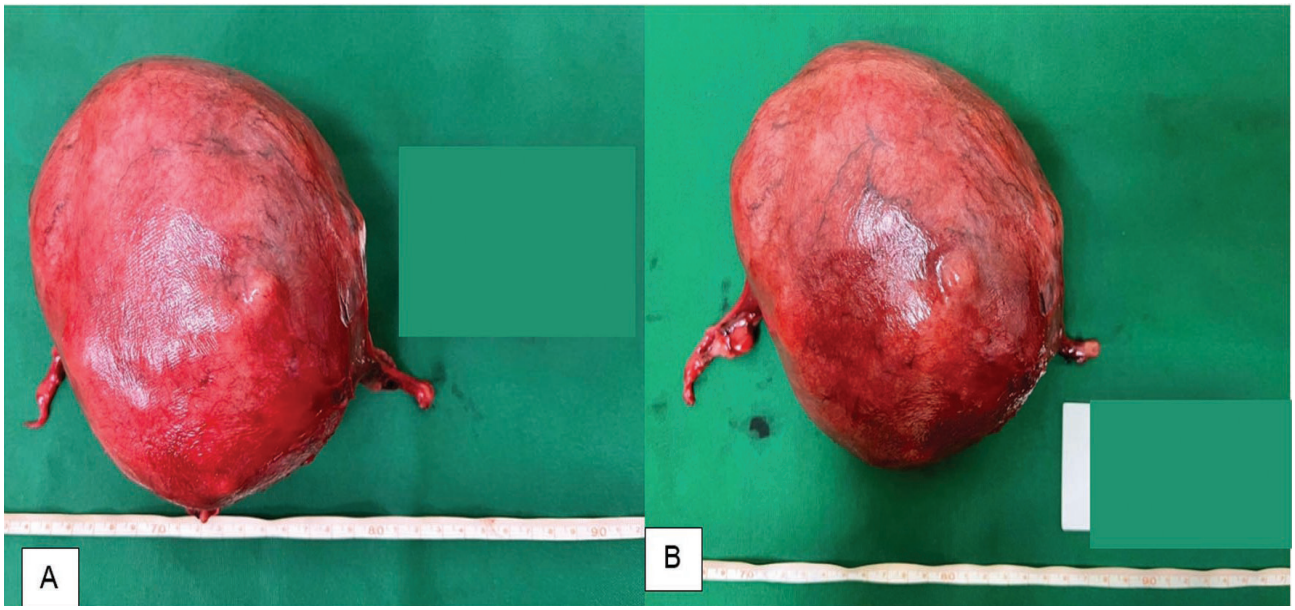

Figure 8. Anterior (A) and posterior (B) views of the uterus, right and left fallopian tubes, right and left ovaries.

medications were given. The rest of the hospital stay was unremarkable and patient was discharged improved on the fourth hospital stay. The final diagnosis of the patient was Nulligravid, Myoma uteri, Turner syndrome, mosaic type.

Late onset congenital adrenal hyperplasia, status post Total abdominal hysterectomy with bilateral salpingo-oophorectomy. Patient is co-managed by the Internal Medicine service for management of CAH.

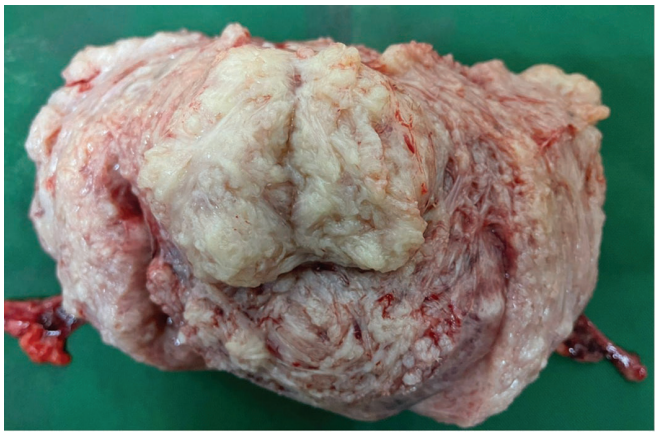

Figure 11. Cut section image of uterus.

Discussion

In the Philippines, the most commonly seen sex chromosome abnormality is Turner Syndrome (TS), accounting for 80.1% of cases, 38.9% of which is the classical type and 25.4 is the mosaic type.[4] The most common form of mosaicism is 45,X/46,XX which includes both the cell line with the normal karyotype and the pathological cytogenetic structure. The incidence of 45,X/46,XX mosaicism in the general female population was estimated at 3.1-3.5%.[5] Homer, et al. (2010)[6], found that patients with mosaicism of 30% 45,X cells or less still present with phenotypical features of TS but had spontaneous menarche. This is further supported by a study done by Pasquino, et al. (1997)[7] which found significant number of patients with mosaicism still undergo complete spontaneous puberty. The index patient had some features of Turner syndrome such as webbing of the neck and broad chest with widely spaced nipples. Likewise, her karyotyping showed mosaic 45,X/46, XX with less than 10% 45,X cells in an adult. This patient, however, had no menarche, and presented with clitoromegaly, virilization of pubertal onset, and with elevated androgen levels in the absence of XY cell line. This led the examiner to think of a concomitant adrenal pathology.

Congenital adrenal hyperplasia (CAH) is caused by an enzymatic defect resulting in decreased cortisol biosynthesis. The severe form of CAH is the most common cause of sexual ambiguity in the newborn.[8] The milder blockage of 21-hydroxylase activity usually does not produce the physical signs associated with hyperandrogenism until after puberty. Thus, this condition, known as late-onset congenital adrenal hyperplasia (LOCAH), is associated with the development of hyperandrogenism in a woman in the second or early third decade of life.[1] Patients with LOCAH usually present with post pubertal onset of virilization, hirsutism, clitoromegaly, and amenorrhea. They commonly have a history of prepubertal accelerated growth, with later decreased growth and a short ultimate height,[8] all of which were present in the index case. Laboratory examination of patient revealed an elevation of 17-hydroxyprogesterone and testosterone which further supports this diagnosis.

It is difficult to hypothesize a theory to explain the co-existence of TS and CAH in a patient with primary amenorrhea. Only about seven cases of rare association of TS and CAH have been reported in literature, and this is summarized in table 2. Concomitant existence of TS and CAH, particularly the late-onset type, may be associated with some problems. First, diagnosis becomes difficult due to the confounding presence of the typical signs such as amenorrhea, short stature, and hirsutism. Thus, karyotyping during investigations of patients with ambiguous genitalia or those with diagnosis of CAH, may reveal the presence of concomitant TS.[9] Second, the final adult height of patients with concomitant TS and CAH may deteriorate over time due to both diseases. The unopposed hyperandrogenism caused by CAH may lead to an initial skeletal maturation,[10] as seen as a growth spurt in the present case. However, it can mask the growth disorder due to the premature closure of growth plates leading to a short final height, also seen in the index case. Third, early detection and diagnosis is the key in management of both syndromes. The primary treatment for patients with TS is growth hormone therapy to maintain body stature and to allow puberty to begin at par with the age group. Patients with LOCAH may be

treated with glucocorticoids to suppress the adrenal hormones and to prevent rapid growth. The primary goal of treatment is to relieve the patient from the hyperandrogenic symptoms.

The index patient was born, identified and was raised as a female. She had a normal childhood development. During the adolescent phase, she didn't demonstrate any pubertal development and subsequently there was no menarche. Instead, there was the appearance of masculine features such as hair on the upper lip and chin, deepening of the voice, increase in muscle mass, and receding hairline. Ultimately, there was an enlargement of the clitoris. The patient eventually conformed to a male gender identity and role and was attracted to females. A few studies have determined the gender identity of patients with LOCAH. Data showed that there is a significant increase in difference in gender identity and sexual orientation compared to the normal population.[11] The affected patients also had higher masculinization score on several gender-related behavior measures.[12] It was hypothesized that the difference in gender identity and sexual orientation among patients with LOCAH could be due to the exposure to excess androgens which was too subtle to cause anatomical abnormality at birth but nonetheless mild enough to cause hormonal imbalance of the brain thereby later affecting gender identity, sexual orientation, and gender related behavior during puberty and adulthood.[11] The index patient was not alarmed by the lack of menarche and the presence of hyperandrogenic bodily changes, thus no consult was done, and patient had missed out on the opportunity of managing her short stature and improving her pubertal development. Patient eventually identified as a male during the adulthood. Hence, further leading to the patient being undiagnosed for decades. Diagnosis was only made serendipitously when patient came in for hypogastric pain associated with an enlarging palpable hypogastric mass.

Conclusion

Healthcare providers, especially those providing gynecologic care, should be made aware of the possibility of a clinical condition characterized by the coexistence of Turner Syndrome and Congenital Adrenal Hyperplasia, so that early diagnosis and a timely referral to appropriate services may be done to start proper treatment without delay.

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