Cryptomenorrhea in a Case of a 20 year old Nulligravid with Mullerian Anomalies and Concomitant Turner Syndrome Variant

Lizel Del Espiritu Santo - Enguillo, MD; Leedah Rañola-Nisperos, MD and Enrico Gil C. Oblepias, MD, FPSREI
Section of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

A 20 year old nulligravid, presented with primary amenorrhea, short stature, multiple exostoses and delayed mental development. She complained of cyclic pelvic pain. Her karyotyping showed 46, X.t(X;8)(q24;q22). Pelvic ultrasound done on her showed a diagonal vaginal septum, hematosalpinx and hematotrachelocolpos. On exploratory laparotomy, she also had a unicornuate uterus with hematometra and a non-communicating, non-functioning right rudimentary horn. Hysterectomy was done on this patient.

In a review of available literature, this may not be the first case reported to describe occurrence of congenital reproductive tract anomalies in combination with gonadal dysgenesis. However, this is a case with a rare combination of congenital anomalies. Its possible pathogenesis, treatment and implications on the patient's reproductive future are discussed.

Key words: Turner syndrome, hematosalpinx, hematotrachelocolpos, unicornuate uterus, rudimentary horn

Introduction

Gonadal dysgenesis results from a developmental anomaly during embryogenesis caused by chromosomal aberrations, mosaicism or mutation-deletions in the short arm of the second X chromosome. Gonadal dysgenesis is a cardinal feature of Turner Syndrome (TS), 95 – 98% of affected patients are infertile (Singh and Carr 1966; Weiss, 1971; Lippe, 1996) and 90 % will require hormonal replacement therapy. It has been hypothesized that the manifestation of TS are due either to the absence of two normal sex chromosomes before X-chromosome inactivation or to haploinsufficiency of genes in the pseudoautosomal regions of the X chromosomes.[1,2]

In most patients with TS, the diagnosis is usually delayed often made during adolescence when they fail to enter puberty or in adulthood because of lower than average height. The frequency of physical abnormalities in Turner syndrome varies with the pattern of the karyotype. According to a study, the diagnosis is made an average of seven years after short stature is clinically evident on the female growth charts. In a case series, 4 percent of girls referred for genetic evaluation of isolated short stature were diagnosed of having Turner syndrome. The chromosomal region and genes that account for the physical characteristics of TS remain uncertain.[3,4,5] Turner syndrome occurs in 1 out of 3000 live births. It is even rarer to see patients with Turner syndrome with reproductive tract anomalies resulting in menstrual obstruction or cryptomenorrhea. In this article, we are presenting a case of a Turner syndrome variant with cryptomenorrhea secondary to a diagonal vaginal septum and a unicornuate uterus with non-communicating, non-functioning right rudimentary horn.

The Case

P.V. is a 20 year old from Sorsogon admitted because of cyclic pelvic pain. Her past medical history and family history were unremarkable.

She is an elementary school graduate, with no vices. She is unemployed, still living with her parents and dependent on them for support. Her father is a farmer, and the sole bread winner in family. She denies having had coitus, smoking, alcoholic intake and illicit drug use. She has never menstruated.

The patient started having cyclic pelvic pain six months prior to admission. For this, she consulted a private physician who requested for a transrectal ultrasound to be done on her. The ultrasound revealed multicystic adnexal masses, most likely ovarian in origin and a non-visualized uterus. These led to the referral to our institution and her travel to Manila for further evaluation and management.

On physical examination, she was anxious and had delayed verbal response. She was 120 cm tall, weighed 30.2 kg, and had a BMI of 20.9. She had dysmorphic features. Her posterior hairline was low. She had multiple exostoses and an increased carrying angle of the right wrist and the flexure of the left upper extremity. The 4th toe on the left foot was proximally inserted, while 2-3 toes on the right foot had mild syndactyly. Her secondary sexual characteristics were Tanner stage 5 for both breast development and pubic hair distribution (Figure 1). On abdominal examination, a vague mass on the right hypogastric area was palpable and was slightly tender. On inspection, the patient had normal external genitalia. There was note of a diagonal septum in the vaginal canal extending from the right side of the inner third to the left side of the outer third of the vaginal wall completely covering the cervix. Rectal examination revealed good anal sphincter tone and no intraluminal masses. Anteriorly palpable 3 cm from the anal verge was a slightly tender cystic structure measuring 7.0 cm x 5.0 cm x 4.0 cm. There was note of stool on the examining finger.

A transperineal and a transrectal ultrasound done showed a longitudinal hypoechoic band posterior to the urethra and anterior to the rectum measuring 3cm long and 0.5cm thick. Superior to this band was a medium level echo fluid collection 221cc in volume extending up to and dilating the endocervical canal. The uterus was retroverted, pushed superiorly up to the level of the umbilicus and deviated to the left measuring 7.2cm x 4.1cm x 3.4cm. The cervix was dilated and measured 2.6cm in length. The endometrium was hyperechoic measuring 0.5cm with intact subendometrial halo. The right ovary measured 2.3cm x 1.5cm x 1.4cm. Inferior to the right ovary was a thin-walled, unilocular anechoic cyst measuring 2.7cm x 2.9cm x 2.5cm. The left ovary measures 3.1cm x 2.1cm x 2.1cm with largest follicle measuring 0.8cm. Lateral to the left ovary was a tubulo-cystic mass measuring 6.3cm x 3.3cm x 3.3cm with low level echo fluid and incomplete septations within. There was no free fluid in the pelvic cavity. The ultrasound impression was hemato-trachelocolpos with longitudinal vaginal septum, normal uterus with thin endometrium, right adnexal cyst, consider paratubal vs. paraovarian cyst, left adnexal mass, consider hematosalpinx.

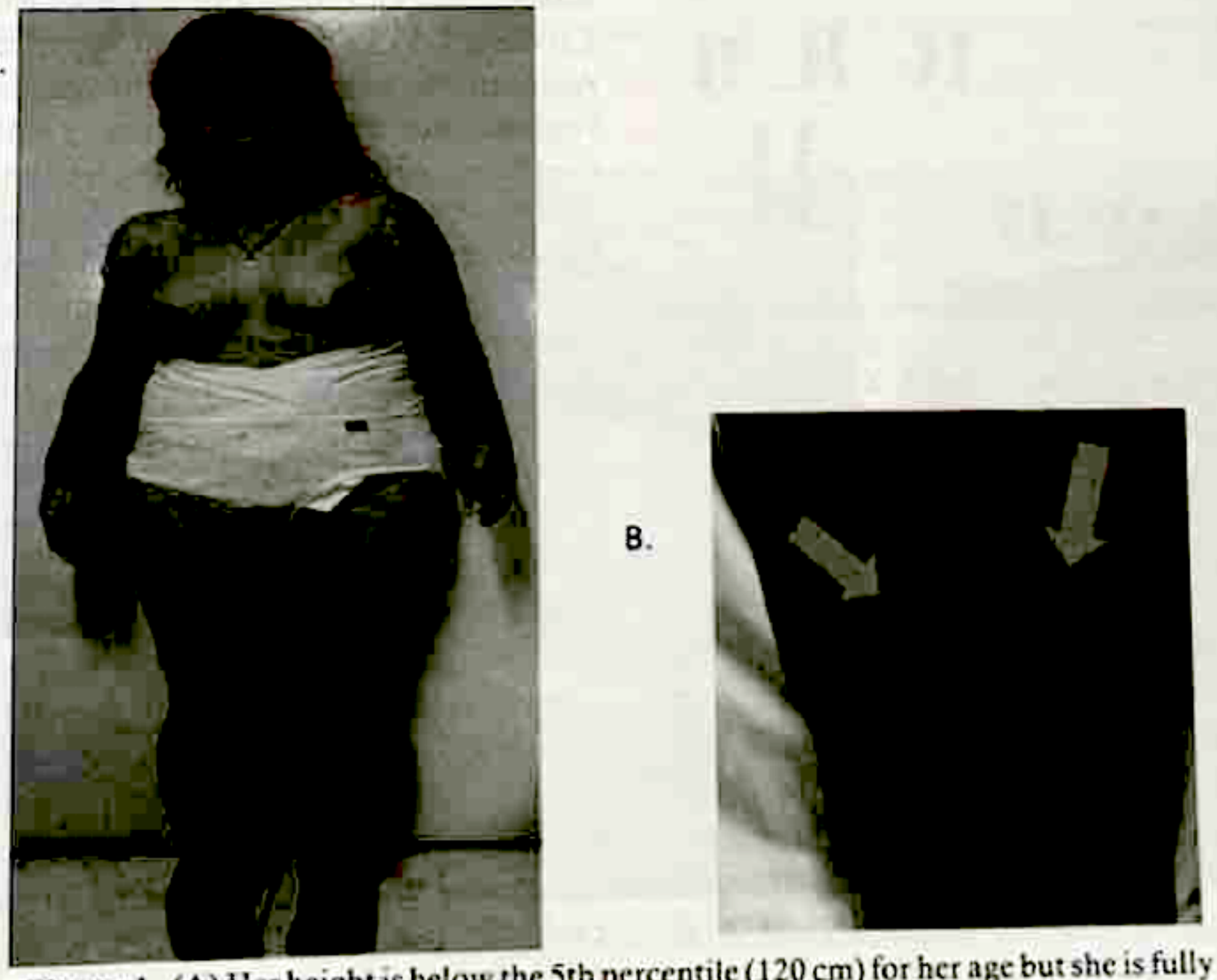

Figure 1. (A) Her height is below the 5th percentile (120 cm) for her age but she is fully developed with Tanner stage 5 (B) Lower extremities with multiple exostoses.

Karyotyping revealed 46, X,t(X;8)(q24;q22), a Turner syndrome variant (Figure 2). Ultrasound of the whole abdomen showed normal scan of liver, pancreas, spleen, kidneys, urinary bladder, a non-dilated biliary tree, and a contracted gallbladder. 2D echocardiogram showed normal sized left ventricle with adequate wall motion and contractility and preserved overall systolic function, mild tricuspid regurgitation, pulmonic regurgitation and ejection fraction of 80%. Chest x-ray showed unremarkable cardiopulmonary findings. Skeletal survey showed findings suggestive of hereditary multiple exostoses of the hemivertebrae T5, T6 and T7 and T10-T12, compression deformity of the T3 and T12. A central DEXA bone scan to assess bone age and density was not done due to limited resources. Peripheral serum assay for FSH showed 4.7 mIU/L, LH 2.7 mIU/L, serum estradiol level of 59.6 mIU/L, FT4 14.7 mIU/L, TSH 0.7 mIU/L, all within normal limits. CBC with platelet, FBS, urinalysis, serum electrolytes, PT/PTT results were likewise all within normal limits. Her blood type was O+.

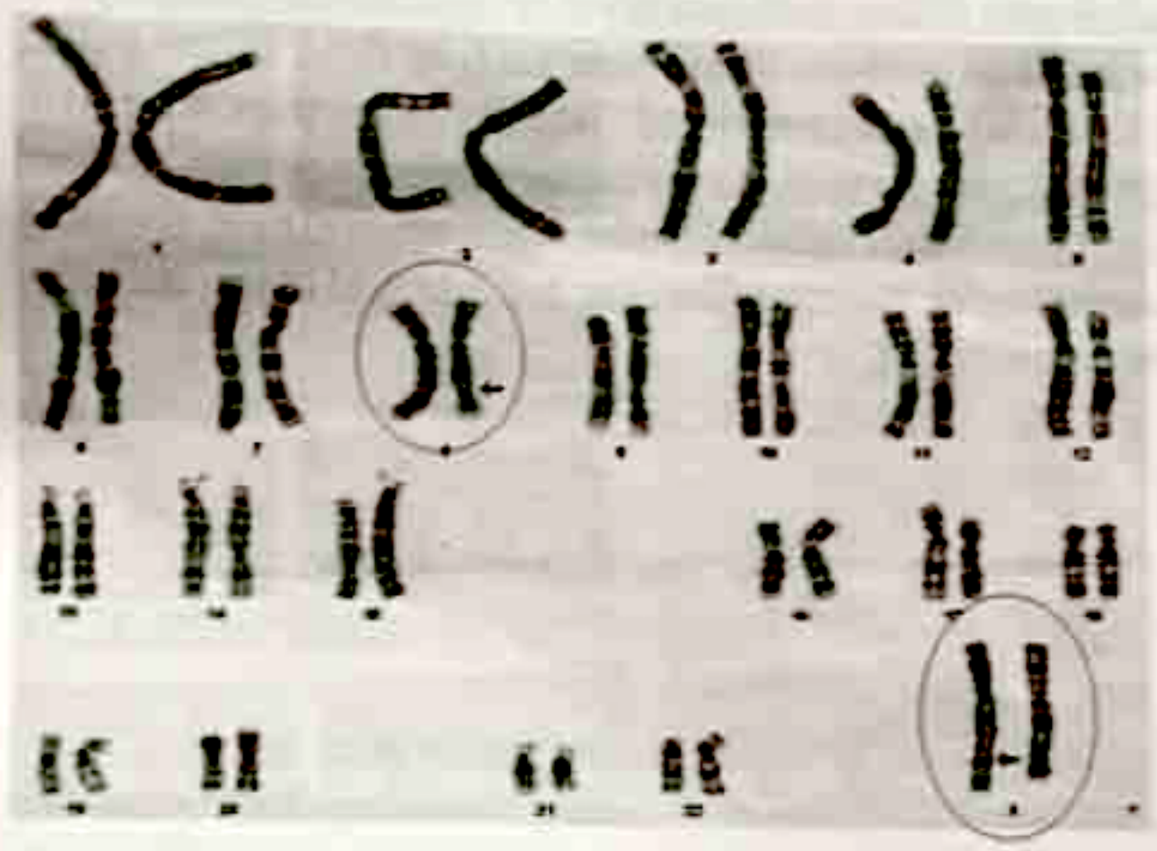

Figure 2. Karyotyping result of our index patient shows 46,X,t(X;8)(q24;q22). A balanced translocation between chromosome X and 8 with breakpoints at bands Xq24 and 8q22.

The patient was referred to Psychiatry. She was diagnosed with mild mental retardation with delayed cognitive and verbal responses. She is capable of doing activities of daily living, but with direct supervision from a guardian. The patient was also co-managed by the Department of Internal Medicine and the Genetics Section. The pre-operative working impression was: Cryptomenorrhea secondary to a diagonal vaginal septum; Hematosalpinx, right; Turner syndrome variant; Mental retardation, mild.

For the menstrual obstruction, an excision of the diagonal vaginal septum was recommended. In the process of counseling and securing of the consent, the family was informed of the following: the post-operative care needed to be undertaken to keep the vagina patent after the procedure; the chances for repeat surgery for vaginal stricture due to wound contracture; and the patient's prospects of future pregnancies. The father decided on a hysterectomy instead, to which the patient had no objection.

Intraoperatively, there was no ascitic fluid. The liver, gallbladder, subdiaphragmatic surface, stomach, spleen, bilateral kidneys, omentum and intestines were smooth and grossly normal on palpation and on inspection. There were no palpable or enlarged paraaortic and pelvic lymph nodes. The vagina was enlarged and very much dilated. Connected to its left was a uterus with an enlarged fallopian tube with an indurated proximal segment and a dilated clubbed distal end. Connected to its right is a fibromuscular band with a nodular rudimentary horn with an attached normal looking fallopian tube. A total hysterectomy, excision of the rudimentary horn and left salpingectomy were done. Both ovaries were grossly normal and along with the right fallopian tube were left in place.

The uterus measured 6.0 cm x 4.5 cm x 2.5 cm with smooth serosal surface. On cut section, it contained 150 cc of blood. The myometrium measured 2.5 cm at the anterior fundal wall. The endometrium measured 0.3 cm and was smooth and spongy. The uterine cavity measured 5.0 cm, 1.0 cm of which was the endocervical canal. The cervix was smooth and short and deviated to the left measuring 1.0 cm x 1.5 cm x 1.0 cm and appeared grossly normal. Adjacent to the right side of the uterus was the proximal vaginal canal with a smooth cavity wall which on cutting contained 70 cc of blood. It measured 4.0 cm x 3.0 cm x 3.0cm. Attached to the right side of the vagina is a fibromuscular band measuring 3.8 cm x1.5cm x 1.5cm connected to a small knobby rudimentary horn measuring 1.0 cm x 1.0 cm x 0.5cm with no endometrial lining on cut section. The left fallopian tube was firm on palpation and was dilated to 8.0 cm x 3.o cm x 2.5cm which contained old blood clots (Figures 3 & 6).

The final diagnosis was: Cryptomenorrhea secondary to a diagonal vaginal septum; Hematosalpinx, left; Unicornuate uterus with non communicating non functioning right rudimentary horn; Turner syndrome variant; Mild mental retardation.

Post operative vital signs were stable. The rest of the hospital stay was unremarkable. Patient was discharged on the 4th hospital day.

Histopathologic examination showed secretory phase endometrium, chronic cervicitis with squamous metaplasia, fibromuscular wall for specimen labeled

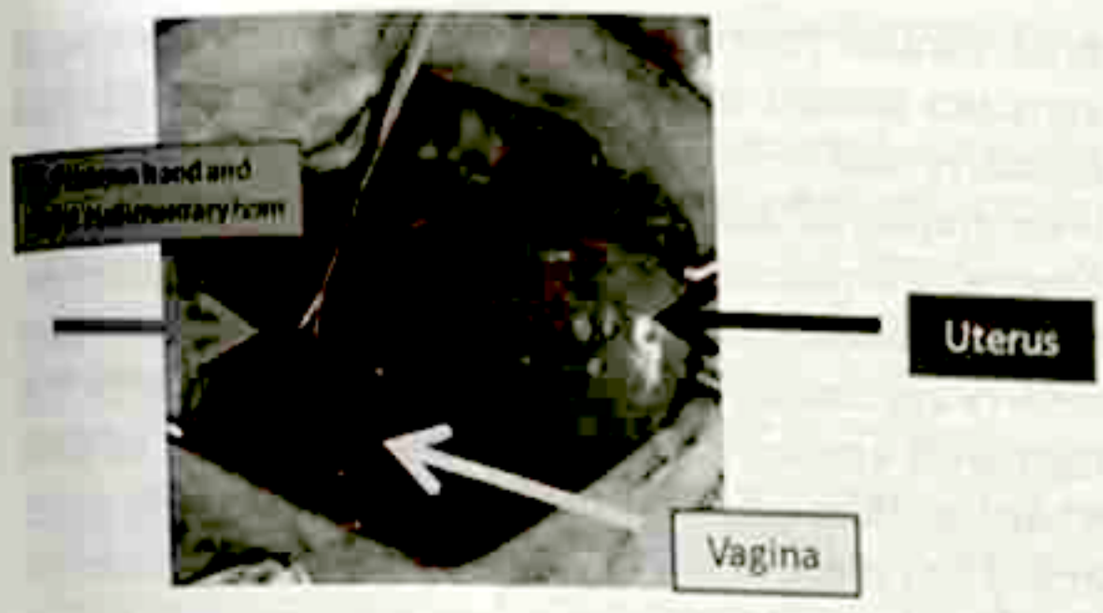

Figure 3. The uterus deviated to the left, filled with hematometra on cut section.

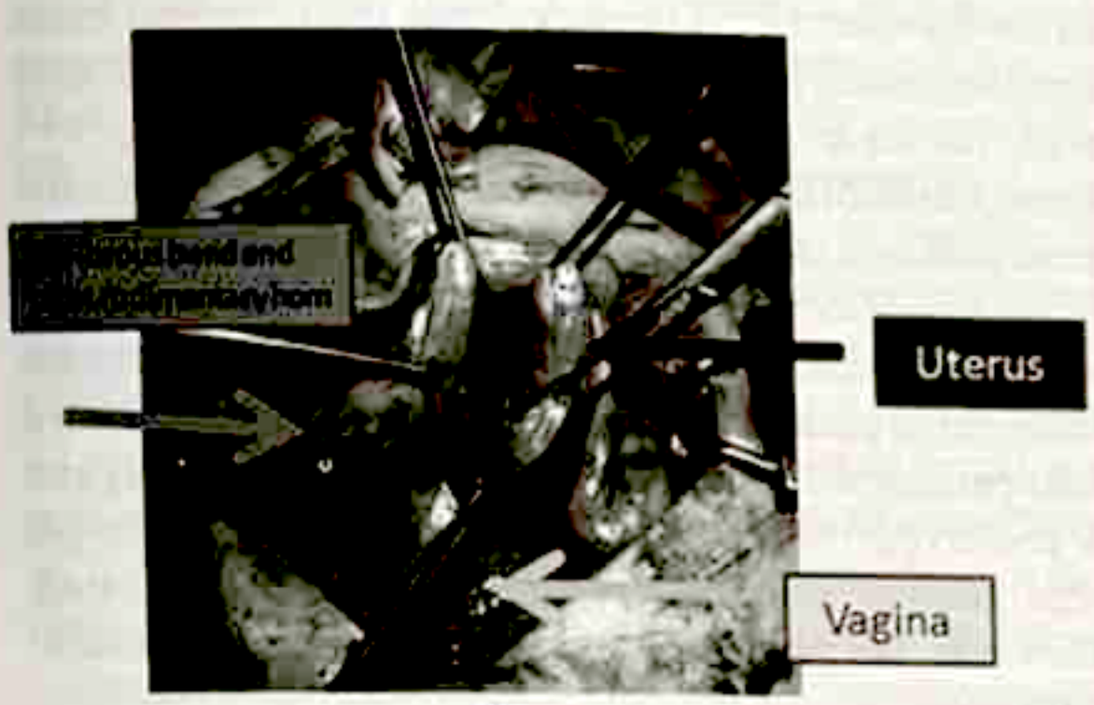

Figure 4.

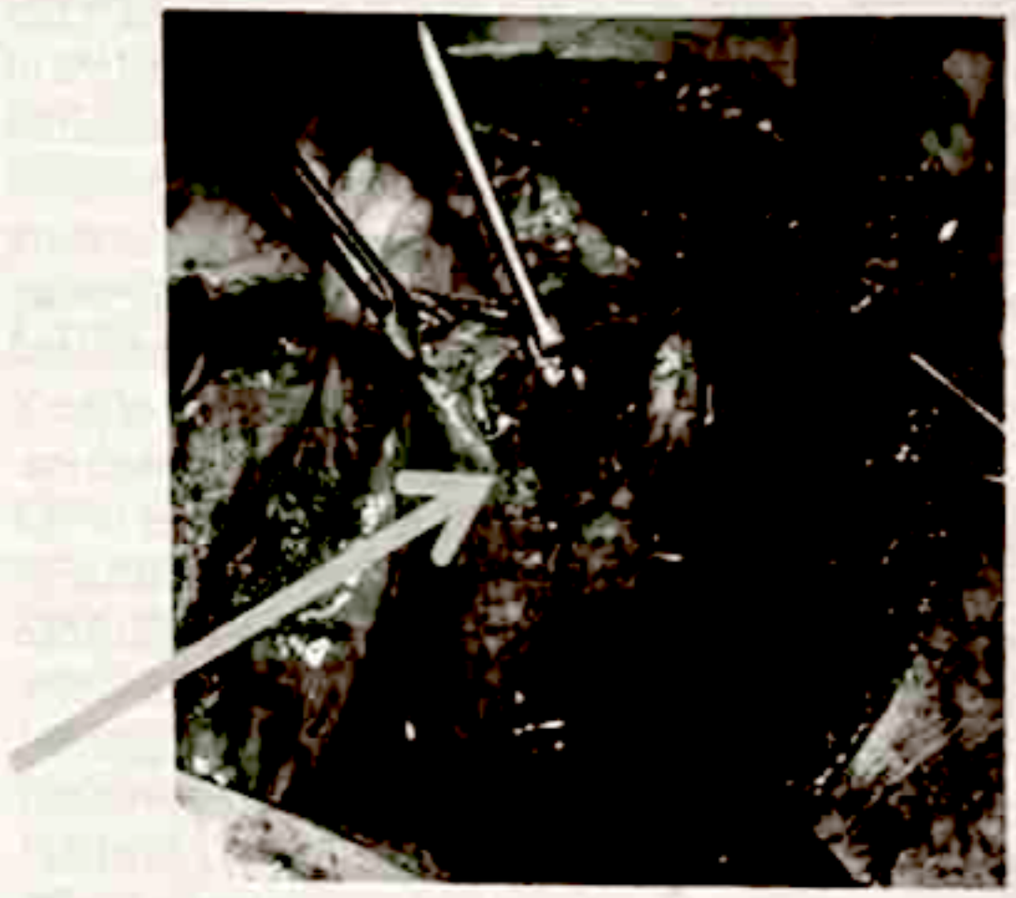

Figure 5.

Figures 4 & 5. Adjacent and distal to the uterus is the vagina with hematocolpos. On the contralateral side is the right rudimentary horn connected with a fibrous band.

uterus; fibromuscular tissues, no endometrial tissues and stroma seen in specimen labeled fibrous band and rudimentary horn; fibromuscular tissue with hemosiderin laden macrophages consistent with old hematosalpinx for specimen labeled left fallopian tube.

Discussion

Turner syndrome is a genetic disorder characterized by the absence of all or part of a normal second sex

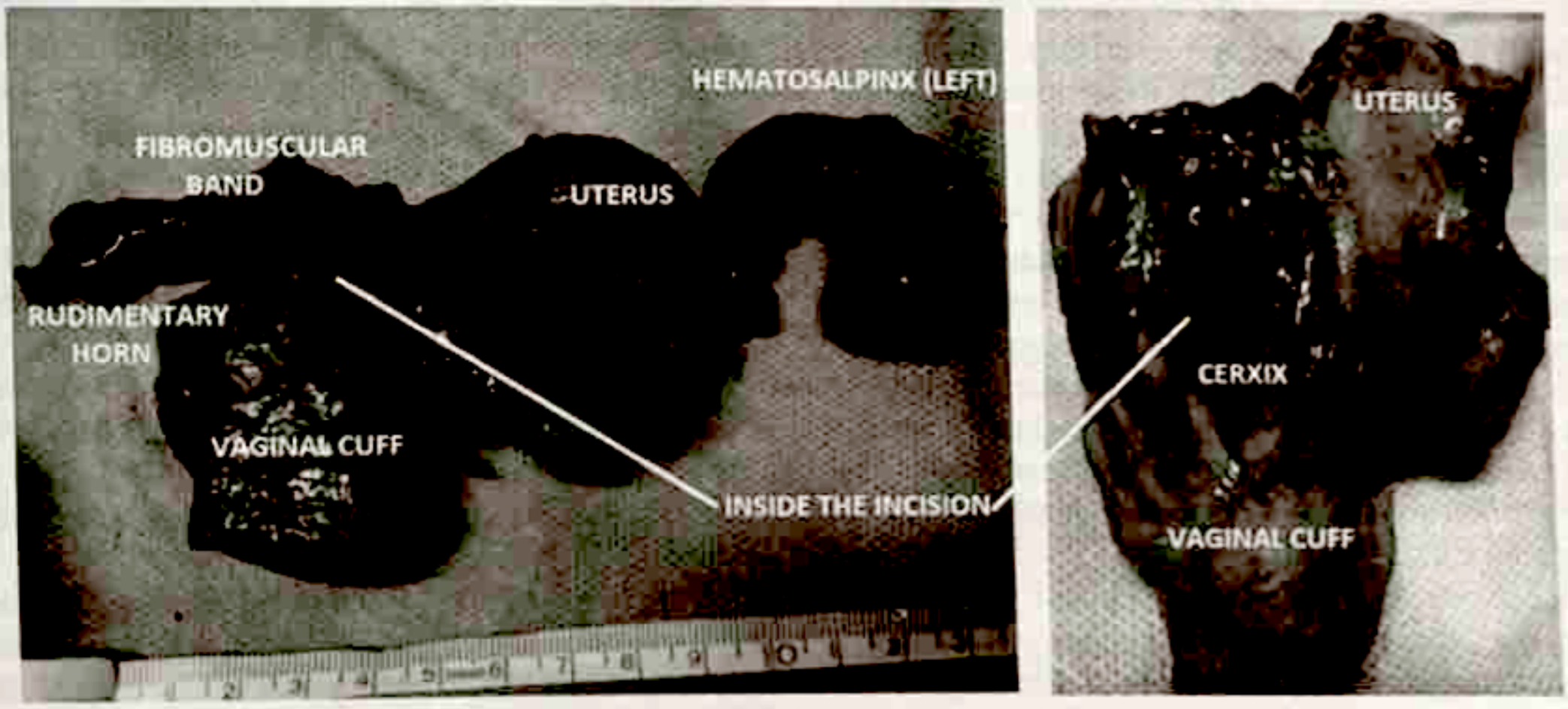

Figure 6. The specimen showing right rudimentary horn, the left hematosalpinx, the cut section of the unicornuate uterus and the cervix through the incision on the vaginal cuff.

chromosome that leads to a constellation of physical features that often includes congenital lymphedema, short stature, gonadal dysgenesis and polymalformations (possibly of the cardiac, renal and skeletal systems). Turner syndrome occurs in 1 out of 3000 live-born girls. Approximately half have monosomy X (45, X), and 5- 10 % have a duplication (isochromosome) of the long arm of one of the X chromosomes, as seen in our index patient. She has balanced translocation between chromosome X and 8 with breakpoints at bands Xq24 and 8q22. Having a 46,X,t(X;8)(q24;q22) karyotype, her condition is a variant of the classic Turner syndrome.

Isochromosomes for Xq are the most common structural abnormality involving the X chromosome. They are found in 1 in 50,000 newborns and in at least 15% of patients with Turner syndrome (Hook and Warburton 1983). About 200 cases of isochromosome Xq with or without mosaicism have been reported in the literature (Kaffe, et al. 1983; Midro, et al. 1988). Most of the other types have mosaicism of 45, X, with one or more additional cell linages.[6,7,8] Both the short and the long arms of the X chromosome contain genes important for ovarian function. The aneuploidy alone may lead to a reduction in the number and survival of oocytes. Loss of interstitial or terminal long-arm material of the X chromosome (Xq) can result in primary or secondary ovarian failure. In utero, the ovaries have already decreased number of primordial follicles. They appear to undergo premature apoptosis that they usually become scarce by the time of adult life.[9] Breast budding, pubic and axillary hair appears in 5 to 25 percent of the cases. Only 2 to 5 percent of the patients will have menstrual cycles before eventually going into premature menopause (Groll and Cooper,1976; Lippe, 1996; Saenger, 1996; Hovatta, 1999).[10] They usually possess short stature and the typical skeletal changes, probably as a result of the haploinsufficiency of the short stature-homeobox (SHOX) gene located in the pseudoautosomal region of X and Xp.[11]

Although short in stature and with the characteristic dysmorphic features seen in TS, our patient was phenotypically female with Tanner 5 staging. Earlier thought to be amenorrheic, the patient was eventually found to be menstruating with the occurrence of cyclic pelvic pain brought about by the impedance of menstrual flow due to a vaginal septum. Interestingly, this patient also had concomitant mullerian abnormalities, in the form of a unicornuate uterus and a non-functioning, non-communicating rudimentary horn.

Most people with TS have normal intelligence. However, approximately 10 percent of patients, irrespective of karyotype have substantial developmental delays need special education and require continued assistance in adult life.[10] Our patient was diagnosed of mild mental retardation. Although able to perform activities needed in everyday living, she has delayed cognitive and verbal responses. The patient has never been employed and has been fully dependent on her parents. TS patients have relatively poor self-esteem. During adolescence, immaturity, social isolation and anxiety are common.[12] However, most adults with TS react with appropriate depression and feelings of loss related to their physical limitations, but usually cope well. Their sense of self appears to be directly related to their health status.[13]

A cause for health concern for Turner syndrome patients would be cardiovascular in nature. The increased possibility of death from cardiac problems is a serious cause for alarm.[9,10] The prevalence of congenital heart disease among patients with TS ranges from 17% to 45%, with no clear phenotype-genotype correlations.[14,15,16] Coarctation of the aorta and bicuspid aortic valve are the most common structural malformations, followed by other left-sided defects. Hypertension, mitral valve prolapse and conduction defects also occur. 2D echocardiogram done on the patient showed her heart to have normal sized left ventricle with adequate wall motion, contractility and a preserved overall systolic function. Mild tricuspid regurgitation, pulmonic regurgitation was appreciated. However, her ejection fraction is still within normal at 80%.

No intervention was deemed necessary for her skeletal malformations or her genetic aberrancy. Cardiac wise, no added management was recommended for the meantime apart from regular annual medical check-up. Medically, her more immediate concern is the cyclical hypogastric pain brought about by the obstruction of menstrual flow. The choice of surgical management in this case was not straightforward. The option of excising the diagonal vaginal septum was presented. In the course of counseling the patient and relatives, the need for diligent post-operative care to prevent vaginal stricture after surgery was discussed. In procedures requiring the excision of a septum involving the whole circumference of the vaginal canal, contracture of the wound often times result in stricture of the vaginal lumen. This in turn will necessitate a repeat surgery to re-establish the patency of the vagina to again allow menstrual egress in patients with a uterus. It has been reported that 8 - 12 percent of excisions for obstructive vaginal septa needed re-operation, with 1-2 percent eventually resorting to a hysterectomy for a definite solution to the problem.[20,21]

Her parents were apprehensive of the recommended surgery because of the following reasons: the patient cannot take care of the post-operative care herself; the family cannot comply with the required follow-ups without having to stay in Manila longer than they can afford; and

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in case of re-surgery, the family cannot afford to come back to Manila.

With this development, it was pointed out to the relatives that the only other choice was to do hysterectomy. This would mean however, curtailing her reproductive capabilities. It was explained to them that patients with her condition may still be fertile and bring pregnancies to term. However, it was also mentioned that a pregnancy with her cardiac condition may predispose her to morbidities and even mortality associated with maternal obstetric complications. Furthermore, she will need to get pregnant at the soonest possible time if still desirous of bearing children since premature ovarian failure is common if not expected in women with her condition.

Although rare, there is a 2% chance of achieving pregnancy in women with Turner Syndrome, and is most likely to be in those with mosaicism having a normal 46, XX cell lineage, a 47, XXX cell lineage, or very distal Xp, Xq deletions.[14] Thus, our patient may be capable of bearing a child if she so desires. To date, 160 spontaneous pregnancies in 74 women have been recorded (Tarani et al, 1998). The average age of these women at pregnancy was 24 years and not more than 34 years. Most of them have mosaic Turner's karyotype. These women however have an increased risk of spontaneous pregnancy loss. Also, pregnant TS patients are at a higher risk of maternal obstetric complications. Mostly due to their cardiovascular conditions that include cardiac malformations, early-onset hypertension, coronary ischemia, and even aortic defects.[17, 18] There have been five case reports of aortic dissection in women with TS during pregnancy.[10]

Given this information, the patient's parents was even more convinced that a hysterectomy be done on their child instead. They based their decision on the following reasons: the patient is completely dependent on them and is mentally and physically incapable of taking care of herself much more a child of her own; the increased risk of losing the patient to obstetric complications if she does get pregnant; and the realistic appraisal of the not so favorable prospects of the patient getting pregnant soon enough to make good use of the conserved uterus before she goes into premature menopause.

There was no negative reaction from the patient on the contemplated procedure. The patient and her parents were reassured that despite the fact she will not be able to bear children after the surgery, she may still be sexually active if she so chooses since the vagina will be functional even with the septum because of its diagonal orientation.

The patient had the exploratory laparotomy and underwent the hysterectomy as planned. Intraoperatively it was discovered that her uterus had some congenital anomalies as well. A unicornuate uterus with a rudimentary horn is a rare type of mullerian duct malformation. The incidence of unicornuate uterus in mullerian anomalies is 4.4%. The unicornuate uterus is an example of an asymmetric lateral fusion defect resulting in two hemiuteri.[19] One hemiuterus is usually functional as a unit with a fallopian tube and cervix, while the other is incomplete to varying degrees. Usually asymptomatic, this could possibly have gone undiagnosed if not for the cyclic pelvic pain due to the hematometra caused by the vaginal septum.

The patient tolerated the surgery well and was discharged improved. Her guardians were advised of the patient's need for regular cardiac check-up and for serial hormonal monitoring to ascertain actual menopause to determine when to initiate hormonal replacement therapy

To the best of our knowledge, this is the first reported case of a Turner syndrome variant with diagonal vaginal septum and a unicornuate uterus with a rudimentary horn.

Conclusion

In some instances, the choice of management isn't as clear cut as we would want it to be. An anatomic defect may need to be addressed differently than it should have been normally in special circumstances. An obstructive reproductive tract anomaly ideally should be remedied by the surgical removal of the obstruction with the intention of establishing an outflow tract for menstrual egress, a receptacle for coitus, and a passageway for child birth. At times, the defect itself makes correction surgically unfeasible without difficulty or the need for a repeat surgery. Special attention must be given to the post-operative care if the recanalized vagina is to remain patent to allow conservation of the uterus.

However, the circumstances the patient is in sometimes will have to be taken in consideration. This is one such case. Although hysterectomy will render our patient infertile, given the physical and mental status of the patient; her access to continued medical care; and her prospects of future pregnancies, the procedure may just be the better choice for our patient.

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