Peripheral Precocious Puberty with Ovarian New Growth: A Case Report

Andrea Mikaela M. Gavino, MD and Ina S. Irabon, MD, FPOGS, FPSRM, FPSGE
Department of Obstetrics and Gynecology, Ospital ng Makati

Precocious puberty is defined as appearance of secondary sexual characteristics that begins earlier than usual, and may be central or peripheral in origin. It is the physician's duty to undertake a detailed investigation of the cause of the condition so as not to overlook a potentially correctable pathologic lesion, and prevent long-term somatic and psychosocial consequences in the child. This paper presents a case of 10 year old female with clinical signs and symptoms and laboratory results that point to a possible peripheral type of precocious puberty , and with a huge ovarian mass, which intraoperatively yielded inconclusive histopathologic findings due to massive necrosis. This paper aimed to discuss the possible etiologies for the development of precocious puberty in the index case, and the treatment options for both precocious puberty and ovarian new growth.

Key words: Peripheral precocious puberty, ovarian new growth

Introduction

Puberty is influenced by the hypothalamic-pituitary-gonadal (HPG) axis. As such, the axis causes biological changes in the body promoting puberty, ultimately resulting in the possibility of sexual reproduction.[1] Clinically, puberty begins in females with the appearance of breast budding.[2] Physiologically, the normal sequence of events of puberty begins with the development of the breasts. followed by pubic and axillary hair development, after which a period of maximal growth velocity ensues, and ends with the commencement of menarche.[1] Typically, this series of development from initiation of breast budding up until the onset of menarche, takes about an average of 2- 3 years. When these changes appear too early or faster than usual, then one must ponder the presence of precocious puberty.

Precocious puberty is defined as appearance of secondary sexual characteristics that begins earlier than usual,[1] traditionally before 8 years of age in girls and 9 years in boys[3], or at any age that is 2.5 standard deviations earlier than normal.[2] Precocious puberty is classified into two major categories based on the etiology: central precocious puberty (GnRH dependent) or peripheral precocious puberty (GnRH independent).[3]

There are many etiologies for peripheral precocious puberty (PPP), with diverse clinical presentation, resulting from early exposure to androgens, estrogens, or both. The primary goals of therapy are to halt or slow down pubertal development, restore sex steroids to prepubertal values, and attenuate linear growth velocity and rate of skeletal maturation in order to maximize height potential, especially if physicians are able to catch these patients early. Important part also of the holistic management would be to address the possible psychosocial impact of these early bodily changes on the child and help her cope with the social stigma associated with being physically different from her peers.[1]

This case report presents a pediatric patient with clinical manifestations and laboratory work-ups suggestive of a peripheral type of precocious

puberty, but whose final histopathology report revealed inconclusive results due to specimen necrosis. This paper aimed to discuss the possible etiologies for the development of precocious puberty in the present case, with focus on the ovarian new growth present. The objectives of this paper were the following: 1) to discuss peripheral precocious puberty, 2) to discuss the management and treatment options for both precocious puberty and ovarian new growth.

The Case

The authors were presented with a 10-year-old female who came in with a chief complaint of abdominal pain. One month prior to consult, patient noted onset of left lower quadrant pain, stabbing in character, non-radiating, with a pain scale of 6/10. The pain was temporarily relieved by intake of Mefenamic acid and Hyoscine-N-butyl-bromide tablets. Patient also complained of changes in bowel movement, with intermittent symptoms of constipation, relieved by Bisacodyl rectal suppository. In the interim, she noted increasing severity of abdominal pain accompanied by constipation. Her mother brought her for consultation in a private clinic where ultrasound was done and revealed a large multiloculated cystic mass in the right pelvic area with extension to the abdominal area, measuring 19.3 cm by 14.9 cm. She was subsequently referred to this institution for further management.

Patient has no known co-morbidities. Family medical history revealed diabetes mellitus from the paternal side. The patient is a non-smoker, non-alcoholic drinker. She has been regularly menstruating since the age of 9 lasting for 10 to 11 days, using up to 4 to 5 moderately soaked pads per day, not associated with dysmenorrhea. She has no history of sexual contact. Onset of secondary sexual characteristics was noted as follows: thelarche at 7 years old, pubarche and adrenarche at 8 years old, growth spurt and menarche at 9 years old.

The patient lives with her parents, and is currently enrolled as a Grade 4 student in a public school. HEADSS assessment was done and the results are shown in Table 1.

Table 1. HEADSS assessment for our index case.

HOME: Patient lives with her parents and gets along well with both mom and dad. She is closer to her mother
EDUCATION: Patient is currently enrolled in online class. Her favorite subject is science as she wants to be a veterinarian in the future
ACTIVITIES: Patient likes playing Roblox on phone and ipad. She does not watch too much TV. Her next door neighbor comes over from time to time and they play together on their phones
DIET/DRUGS: She likes to focus her meals on rice and meat like chicken, not so much on vegetables. Patient not so much familiar with drugs but knows they are bad for her
SELF ESTEEM/SEXUALITY: Patient is a shy girl, more of an introvert. She likes boys but currently does not have a crush
SAFETY/SUICIDE: Patient knows to wear a seatbelt when riding a car. She is a generally happy but shy girl. No thoughts regarding suicide.

At the emergency room, patient came in conscious, coherent, and ambulatory, normotensive, non-tachycardic, non-tachypneic, and afebrile. She weighed 60 kg, standing at 154 cm (5'1"), with a BMI of 27 kg/m^2 , classified as obesity class 1 (Figure 1). Breast development was at Tanner stage 2, while pubic hair development was at Tanner stage 3 (Figure 2). There was growth of mature hair on both axillary areas (Figure 3). On palpation, the abdomen was soft and flabby with direct tenderness on the hypogastric area. A movable, cystic, tender mass was palpated at the right hemiabdomen, measuring approximately 15cm by 10cm. Abdominal girth during this time was 101 cm. There was no fluid wave appreciated. Visual inspection of the external genitalia showed no masses or lesions, and no clitoromegaly. On rectal examination, patient had good sphincteric tone, empty rectal vault, and no blood per examining finger. The rest of the physical exam was normal. Complete blood count, urinalysis and blood chemistry were requested, specifically, blood urea nitrogen, liver enzymes, electrolytes – which were all within normal limits (Table 2). She was then admitted for further work up and management with an admitting diagnosis of: Pelvo-abdominal mass, probably ovarian new growth, rule out malignancy; Precocious puberty.

Table 3 shows the results for the tumor markers and hormonal profile of the patient. All tumor

Figure 1. Patient weighed 60 kg, standing at 154 cm (5' 1"), with a BMI of 27 kg/m^2, classified as obesity class 1.

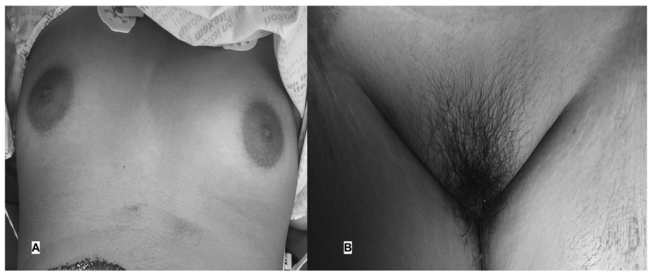

Figure 2. Tanner staging was stage II for breast development (A) and stage III for pubic hair development (B).

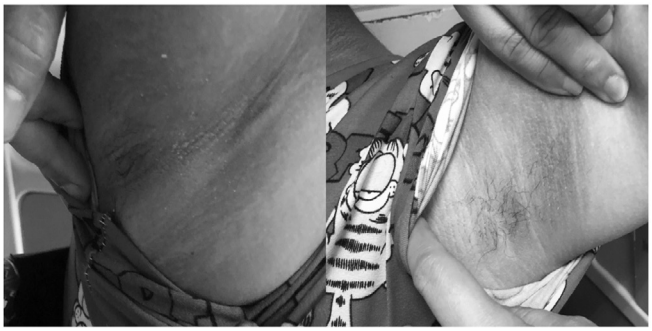

Figure 3. There was growth of mature hair on both axillary areas.

markers were within normal limits, except CA-125, which was slightly elevated at 56.77 U/ml. The tumor marker CA-125, although non-specific for ovarian new growths, is traditionally used to predict ovarian malignancy, but may likewise indicate presence of peritoneal inflammation. The patient's thyroid function tests suggest presence of hypothyroidism, with increased TSH of 6.7 uIU/mL (Normal value: 0.270-4.20 uIU/mL), and decreased FT3 of 3.21 pmol/L (Normal value: 6.1-7.9 pmol/L). Estradiol (E2) level was elevated for age, at 12.73 pg/mL. Prepubertal girls have E2 levels below 10 pg/mL (most <5 pg/mL). LH, FSH, testosterone, prolactin and DHEAS levels were all within normal range. Whole abdominal CT scan with IV contrast (Figure 4) revealed "a large enhancing, multi-loculated cystic mass with thick septations measuring 11.1cm x 16.6cm x 20.3cm (APxTxCC) seen originating from the right adnexal region and extending to the right hemiabdomen just inferior to the liver edge. Inferiorly, the mass is seen extending down to the level of S2 vertebral body, adrenal glands are normal without undue enhancement." X-ray of her non-dominant hand (Figure 5) showed that "bone age matched the reference standard of 13 years and 6 months" (at the time of study, patient's exact chronological age is 10 years and 3 months).

Despite the equivocal CA-125 results (slightly elevated), lack of constitutional signs and symptoms such as weight loss or loss of appetite, and the indolent growth of the mass, the Gynecologic service still considered a possible ovarian malignancy, due to the huge size of the mass and the patient's age. Patient was then prepared for surgery. She was referred to Pediatrics for surgical

Table 2. Baseline laboratories done at the emergency room level.

Complete blood count	**Hgb**	**Hct**	**WBC**	**MCV**	**MCH**	**MCHC**	**S**	**L**	**M**	**E**	**Plt**
	13.6	0.40	14.7	86.1	29.4	34.1	75	17	8	-	395

Urinalysis	**Color**	**Sugar**	**Protein**	**WBC**	**RBC**	**Epithelial**	**Bacteria**
	Dark yellow	Neg	Trace	2.7	1.4	1.7	5.2

Blood chemistry	**BUN**	**Crea**	**BUA**	**AST**	**ALT**	**Na**	**K**
	3.88	50.71	13.42	12.91		139	4

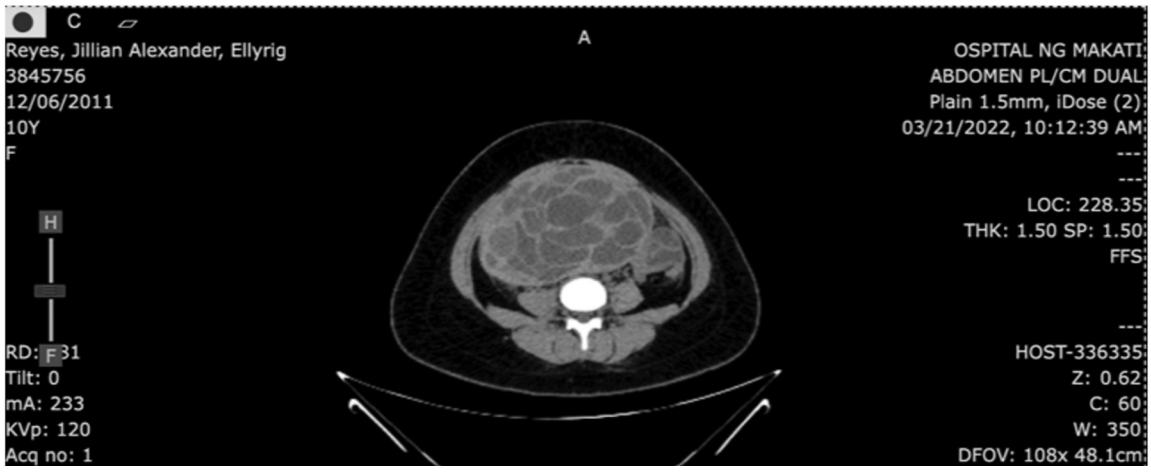

Figure 4. Whole abdominal CT scan with IV contrast showed: A large enhancing, multi-loculated cystic mass with thick septations measuring 11.1cm x 16.6cm x 20.3cm (APxTxCC) is seen originating from the right adnexal region and extending to the right hemiabdomen just inferior to the liver edge. Inferiorly, the mass is seen extending down to the level of S2 vertebral body. Adjacent bowel segments are displaced. Minimal fluid collections are seen in the right paracolic gutter and pelvic region. Prominent to enlarged mesenteric lymph nodes are seen. The largest is anterior to the right kidney measuring 1.7cm x 1.4cm. Adrenal glands, liver, gallbladder, pancreas and spleen are all normal.

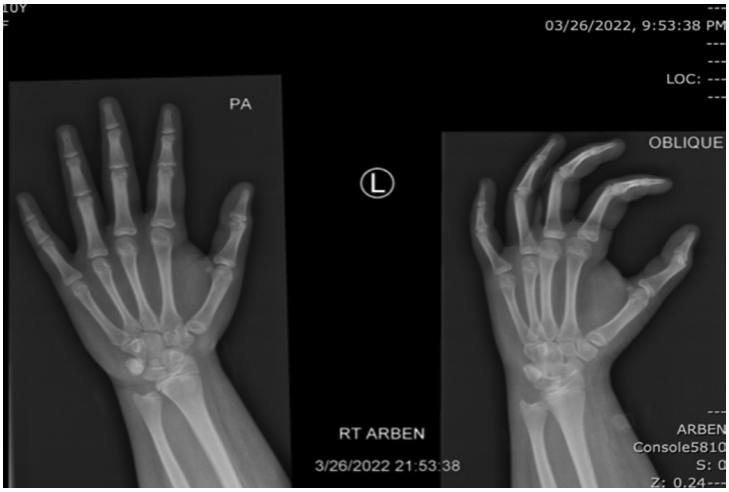

Figure 5. X-ray of her non-dominant hand showed that bone age matched the reference standard of 13 years and 6 months (at the time of study, patient's exact chronological age is 10 years and 3 months).

Table 3. Tumor markers and endocrinologic profile.

Tumor markers		**AFP**	**CA-125**	**CA 19-9**	**CEA**
		<0.500 ng/ml	56.77 U/ml	5.76 U/ml	0.77 ng/ml
Thyroid function tests		**TSH**	**FT3**	**FT4**	
		6.7 uIU/mL	3.21 pmol/L	1.72 pmol/L	
Prolactin	**Estradiol**	**FSH**	**LH**	**DHEAS**	**Testosterone**
11.79 ng/mL	12.73 pg/mL	1.18 mIU/mL	1.10 mIU/mL	1.8 mIU/mL	<0.45 mIU/mL

clearance, and to General Surgery service for possible appendectomy and omentectomy. The operative plan included the following: exploratory laparotomy, peritoneal fluid cytology, left oophorocystectomy and send the specimen for frozen section. If malignancy is confirmed on frozen section biopsy, then surgeons will proceed to omentectomy, possible appendectomy, lymph node palpation (for surgical staging), and possible post-op chemotherapy depending on the stage of the malignancy. On her 4th hospital day, the patient underwent exploratory laparotomy. Upon opening, there was approximately 50cc of bloody ascitic fluid. Peritoneal fluid cytology was done. The left ovary was converted to a 24cmx19cmx6cm globally necrotic, non-foul-smelling, hemorrhagic mass, which was twisted 4x around its pedicle (Figure 6). There was no residual normal ovarian tissue noted (Figure 7). The entire length of the left fallopian tube was likewise necrotic. The right ovary was normal. Due to the massive necrosis and the absence of normal residual ovary, the surgeons opted to do left salpingooophorectomy instead. Frozen section was deferred due to the necrotic tissues. There were incidental findings of right paratubal cyst measuring 4cm x 4cm x 2cm, and a clubbed right fallopian tube (Figure 6). Surgeons hence proceeded with cystectomy of the right paratubal cyst, and right salpingotomy; the paratubal cyst had a thin capsule with clear serosanguinous fluid within. Since Gynecology service considered preoperatively a possible ovarian mucinous tumor and malignancy, an intraoperative referral to surgery was done for appendectomy and omental biopsy. Estimated blood loss was 800 cc. Post-operatively, the patient recovered well and was discharged stable on her 8th hospital day. Final diagnosis was: Nulligravid; Ovarian New Growth, Left; Tuboovarian torsion; Precocious Puberty; Hypothyroidism; Obesity Class 1; status post Exploratory Laparotomy, Peritoneal Fluid cytology, Left salpingooophorectomy, cystectomy of the right paratubal cyst, right salpingotomy, appendectomy, omental biopsy under general endotracheal anesthesia.

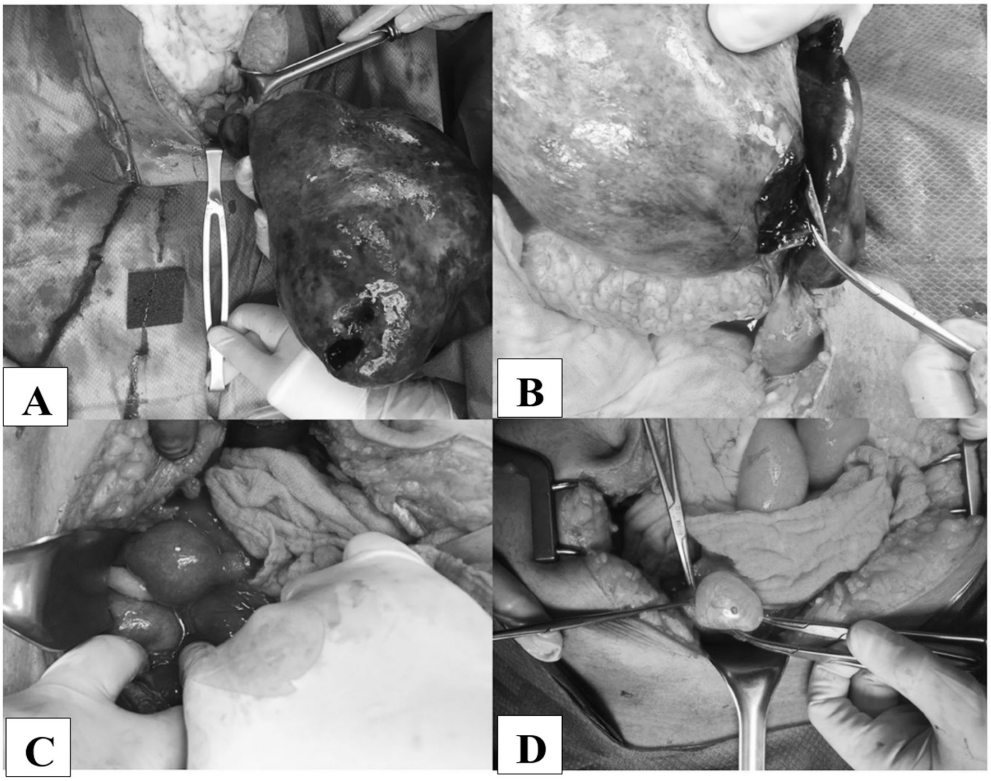

Figure 6. The left ovary was converted to a 24cm x 19cm x 6cm globally necrotic, non-foul-smelling, hemorrhagic mass, which was twisted 4x around its pedicle. There was no residual normal ovarian tissue noted. The entire length of the left fallopian tube was likewise necrotic The right ovary was normal (A and B). There was a right paratubal cyst measuring 4cm x 4cm x 2cm, and a clubbed right fallopian tube (C and D).

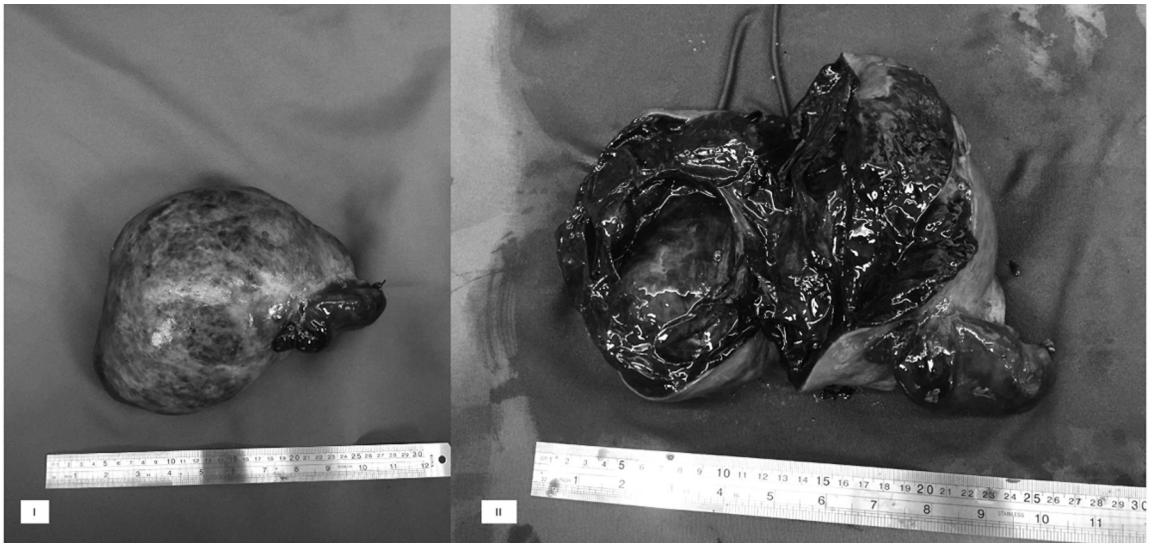

Figure 7. Grossly, the left ovary was globally necrotic, with no residual normal ovarian tissues noted.

Histopathology results revealed the following results: 1) Left ovary and left fallopian tube: salpingooophorectomy - hemorrhagic necrosis involving both left ovary and left fallopian tube (no viable tissue present precluding histologic identification of the neoplasm) 2) Paratubal cyst, right: cystectomy - consistent with paratubal cyst 3) Appendix: appendectomy - acute and chronic periappendicitis 4) Omentum: omentectomy - omental tissue with extensive fibrosis, acute and chronic inflammation, and reactive atypia. Cytopathology of peritoneal fluid revealed "cytomorphologic features consistent with acute and chronic inflammatory pattern, mild".

Patient followed up at the outpatient department post-operatively, with good wound-healing and no subjective complaints. Patient and her parents were carefully advised about the results of all the laboratory tests and intraoperative findings, and the need for regular follow-up check-ups. The family was also advised to seek professional psychosocial counseling and support for the patient as part of the multidisciplinary treatment approach for precocious puberty. The patient's hypothyroidism is presently managed by the Pediatric department.

Discussion

Precocious puberty is the earlier development of secondary sexual characteristics. There are two types of precocious puberty: Gonadotropin releasing hormone (GnRH) dependent type also known as complete, central or true precocious puberty, and GnRH-independent type, also known as incomplete, peripheral or pseudo-precocious puberty.[1,4]

In managing cases of precocious puberty, the physician should undertake a detailed investigation of the cause of the condition so as not to overlook a potentially correctable pathologic lesion. Management of such cases usually revolve around two primary concerns of parents: 1) social stigma associated with the child being physically different from her peers; and 2) the diminished ultimate height caused by the premature closure of epiphyseal growth centers.

Central Precocious Puberty

In this type of precocious puberty, the HPG axis matures earlier than usual and is more common among girls.[5] A major etiology of central precocious puberty in about 80% of the cases, is idiopathic.[1] There are no abnormalities involving the normal process of puberty, other than the fact that there is early development of secondary sexual characteristics, which means both menstrual pattern and fertility remain unaffected.[1] This is traditionally diagnosed with baseline LH levels of more than 5 mIU/L. Index patient had baseline LH levels at 1.10

mIU/L, which can thereby point to a non-central origin. About 20% of cases of central precocious puberty may be attributed to central nervous system lesions. However, the present case did not have any signs nor symptoms that point to a possible central nervous pathology. Primary hypothyroidism may also be a rare etiologic cause for central precocious puberty through diminished negative feedback of thyroxine, resulting in an increased production of TSH, which may be accompanied by an increase in production of gonadotropins, leading to Van Wyk–Grumbach syndrome. This however, generally results in bone retardation.[1] For the present case however, she presented with hypothyroidism but with advanced bone age (bone age 2-3 years older than expected for a 10 year old). Treatment for central precocious puberty is the use of long-acting agonists of GnRH.[6]

Peripheral Precocious Puberty

This type of precocious puberty does not depend on the pulsatile secretions of the HPG axis and instead may be due to other endogenous sources of steroidal sex hormones, as well as exogenous sources[3], thus the term "peripheral". Tumors that produce sex steroids are a common etiology of this type of puberty, particularly those tumors that originate from the ovary, such as germ cell or granulosa cell tumors (produce estrogen and stimulate its release)[1], and the adrenals which may produce androgen-producing tumors.

Germ cell tumors are the most common pathologic or malignant ovarian cysts in the pediatric age group.[7] Germ cell tumors secrete estrogen, and thus may cause bodily changes that manifest as early development of secondary sexual characteristics and abnormal uterine bleeding.[1] Tumor markers such as CA-125, CA 19-9, CEA, LDH and alpha fetoprotein (AFP) are measured to predict chances of malignancy for ovarian tumors, but are not very highly specific for ovarian malignancy. Tumor markers are usually used as ancillary tests in diagnosing ovarian tumors, namely, CA-125 for epithelial tumors and granulosa cell tumors, AFP for germ cell tumors, and LDH for dysgerminoma.[7] A study by Taskinen, et al.[8] in 2015 showed that highly elevated serum levels of either AFP or CA-125, or both (2.7 to 3.5 times the highest reference value) was positively associated with malignant ovarian tumors. In the present case, the CA-125 was just slightly elevated, with the rest of the tumor markers within normal limits. CA-125 may be possibly elevated due to peritoneal inflammation or irritation brought about by the huge ovarian mass. Despite the equivocal CA-125 results, normal CA 19-9, lack of constitutional signs and symptoms such as weight loss or loss of appetite, and the indolent growth of the mass, the Gynecologic service still opted to preoperatively consider a possible malignancy, due to the size of the mass and the patient's age. Thus, the surgical plan included procedures related to ovarian malignancy staging. It was unfortunate that final histopathologic results for the left ovarian cyst only showed hemorrhagic necrosis, because the lack of viable ovarian tissue precluded histologic identification of the neoplasm. Fortunately, the rest of the specimens showed no tissue evidence of malignancy.

Adrenocortical neoplasms are a common cause of peripheral precocious puberty, such as congenital adrenal hyperplasia and McCune Albright Syndrome (MAS)[3] For the present case, whole abdominal CT scan showed normal adrenal glands, and androgen levels were within normal limits, thus effectively ruling out an adrenal pathology. Exogenous etiologies may be from prolonged intake of exogenous sex steroids, such as hormonal pills. However, patient in the present case, denied taking any form of steroidal nor hormonal medications.

Based on the clinical presentation and the results of her laboratory work-ups, it seems highly likely that the precocious puberty may have possibly originated from a germ cell tumor of the left ovary, despite the inconclusive results on histopathologic investigation. Treatment of peripheral precocious puberty involves eliminating the primary source of excess hormones, which in the present case, was most likely pointing to an ovarian source, thus the need for surgical resection. If exogenous sources of sex steroids are identified, they should be eliminated. Classic congenital CAH is treated with glucocorticoids. In McCune-Albright syndrome, some benefit occurs with blocking the estrogen synthesis using aromatase inhibitors (anastrozole, letrozole) and selective estrogen selective receptor modulator (tamoxifen).[3]

A vital point one needs to always consider in managing precocious puberty is the need for multidisciplinary treatment approach. Not only does one need surgeons, gynecologists and pediatricians at the helm, but also the services of a psychologist or a professional who can provide continuous psychosocial counseling and support for the patient. Literature has shown that children experiencing precocious puberty are at high risk of engaging in high-risk behaviors such as substance abuse, conduct issues, social isolation, truancy, and multiple sexual partners,[3,9] mostly due to social stigma of being different from their peers, self-image concerns and peer-pressure. The present case may have been evaluated using the HEADSS tool to have a "relatively sound and stable psychosocial condition" for now, but may still possibly suffer some social discrimination in the future, thus the need for continuous and consistent psychological support. Patients and their parents, relatives or caretakers should be properly educated about this matter.

Conclusion

Precocious puberty is a rare endocrinologic condition that may be central or peripheral in origin. Treatment will depend on the type of precocious puberty established based on clinical presentation and laboratory work-up. Treatment should not only focus on dealing with or eliminating the etiology. This requires a thorough and multidisciplinary management approach, that includes long-term psychosocial support and counseling to prevent psychological complications in the child. Close monitoring of children with precocious puberty is highly suggested, despite initiation of treatment, as the main concerns of parents revolve around the social stigma of such cases as well as the concern for stunted growth.

References

1. Gershenson DM, Lentz GM, Valea FA, Lobo RA. Comprehensive Gynecology. Philadelphia, PA: Elsevier - Health Sciences Division; 2022.
2. Wei C, Davis N, Honour J, Crowne E. The investigation of children and adolescents with abnormalities of pubertal timing. Ann Clin Biochem [Internet]. 2017; 54(1): 20–32. Available from: http://dx.doi.org/10.1177/0004563216668378.
3. Kota AS, Ejaz S. Precocious Puberty. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
4. Bradley SH, Lawrence N, Steele C, Mohamed Z. Precocious puberty. BMJ 2020 Jan 13;368:l6597. doi: 10.1136/bmj.l6597.
5. Berberoglu M. Precocious puberty and normal variant puberty: definition, etiology, diagnosis and current management. J Clin Res Pediatr Endocrinol [Internet]. 2009 [cited 2022 Aug 13];1(4):164–74. Available from: http://dx.doi.org/10.4274/jcrpe.v1i4.3.
6. Eugster EA. Treatment of central precocious puberty. J Endocr Soc [Internet]. 2019 [cited 2022 Aug 13];3(5):965–72. Available from: http://dx.doi.org/10.1210/js.2019-00036 V Kota AS, Ejaz S. Precocious Puberty. In: StatPearls [Internet]. StatPearls Publishing; 2022.
7. Marginean CO, Marginean C, Chincesan M, Marginean MO, Melit LE, Sasaran V, et al. Pediatric ovarian tumors, a challenge for pediatrician and gynecologist: Three case reports (CARE compliant). Medicine (Baltimore) [Internet]. 2019 [cited 2022 Aug 13];98(16):e15242. Available from: http://dx.doi.org/10.1097/md.0000000000015242.
8. Taskinen S, Fagerholm R, Lohi J, Taskinen M. Pediatric ovarian neoplastic tumors: incidence, age at presentation, tumor markers and outcome. Acta Obstet Gynecol Scand 2015 Apr;94(4):425-9. doi: 10.1111/aogs.12598. Epub 2015 Feb 27.
9. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diab Endocrinol 2016 Mar;4(3):265-74. doi: 10.1016/S2213-8587(15)00380-0. Epub 2016 Feb 4.