Blooming Too Soon: A Case of Precocious Puberty*

Nina Rojana L. Yu, MD, Sabrina Ang-Sy, MD, FPOGS, Emmanuel L. Dagala, MD, FPOGS and Joy J. Bautista, MD, FPOGS, FPSREI
Department of Obstetrics and Gynecology, Manila Doctors Hospital

ABSTRACT

Precocious puberty is the onset of pubertal development at an earlier age than is expected based upon established normal standards. The cause of precocious puberty may range from a variant of normal development (eg. premature adrenarche or isolated premature thelarche) to pathologic conditions with significant risk of morbidity and even death (eg. malignant germ-cell tumor or astrocytoma). A case of an 18 month old female presenting with vaginal bleeding following a previously noted breast enlargement was described. Initial assessment based on the patient's history and physical examination is suggestive of precocious puberty. Hormonal studies indicated normal levels of FSH and LH, with an elevation in estradiol. Radiographic analysis showed a normal bone age. Cranial MRI revealed no abnormal masses. Sonographic evaluation showed bilateral cystic masses in the ovaries. A diagnosis of peripheral precocious puberty associated with functional ovarian cysts was made, and the patient was monitored for progression of pubertal development.

INTRODUCTION

Precocious puberty is defined as the onset of pubertal development at an age 2.5 to 3.0 standard deviations below the mean age of puberty onset. Although some controversy exists regarding the lower limit for age of pubertal onset, the commonly accepted threshold age is 8 years for girls and 9 years for boys (Rosenfield et al, 2000). It occurs more frequently among females, with a recent study based in Denmark reporting that the prevalence of precocious puberty is nearly ten times higher in girls than in boys (Teilmann et al, 2005)

Several factors are known to affect the age of onset of puberty, which occurs earlier in black girls, those with early maternal menarche, low birth weight, obesity in infancy and early childhood, and exposure to estrogenic chemicals (Parent et al, 2003). However, these factors do not significantly affect the normal range of the age pubertal onset in the general population, which has been conventionally defined as between 8 and 12 years for girls, and 9 and 14 years for boys. A revised set of guidelines by the Lawson Wilkins Pediatric Endocrine Society (LWPES) recommended lowering the threshold for normal puberty to 7 years in white girls and 6 years in black, but most clinicians still use the conventional 8 year cutoff for white girls. (Kaplowitz et al, 1999).

There are several benign, non-progressive conditions which are characterized by an isolated precocity in certain secondary sexual characteristics, such as premature thelarche, premature pubarche or premature adrenarche. Progressive precocious puberty, on the other hand, may further be classified based on etiology - central, or gonadotropin dependent precocious puberty, and peripheral, or gonadotropin independent precocious puberty, also called precocious pseudopuberty.

In central precocious puberty, the main mechanism is the early activation of the pulsatile secretion of GnRH by the hypothalamus. The cause is idiopathic in 80% of cases, most of which occur in girls. This contributes to the much higher prevalence of precocious puberty among females (Chemaitilly et al, 2001). Premature activation of the hypothalamus-pituitary-ovary axis may also be caused by lesions of the central nervous system; hence, cranial imaging is necessary even in the absence of overt neurological symptoms. (Ng et al, 2003). The most common CNS lesion to cause precocious puberty in young girls is tuber cinereum hamartoma (Jung et al, 1999), although cases caused by optic or hypothalamic gliomas, astrocytomas and congential mid-line defects have also been reported. Less commonly reported causes of central precocious puberty include specific genetic mutations and even primary hypothyroidism.

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In peripheral precocious puberty or precocious pseudopuberty, the main mechanism is the excess secretion of sex hormones derived either from the gonads, the adrenal glands, or from exogenous sources. This form of puberty may be appropriate for the child's gender (isosexual) or inappropriate, with virilization of girls or feminization of boys (contrasexual). In contrast to central precocious puberty, FH and LSH levels are suppressed, and therefore insensitive to GnRH stimulation. In girls, the most common cause of peripheral precocious puberty is a large, functional ovarian follicular cyst (Fritz et al, 2011).

CASE REPORT

Z.I, an 18 month old girl from Camarines Norte, presented with breast enlargement at 5 weeks prior, which was followed by episodes of vaginal bleeding at 1 week prior to admission. She was initially managed as a case of urinary tract infection at a provincial hospital, but her symptoms remained unresolved despite treatment with unrecalled antibiotics. Upon referral to an OB-GYN, a pelvic ultrasound was done and revealed two ovarian cysts measuring 6.2 x 5.4 cm and 9.2 x 5.6 cm respectively. Her family history, past medical history and the rest of her pediatric history are non-contributory.

Physical examination revealed breast enlargement and nipple development corresponding to Tanner stage 3, with noted pigmentation of the areola (Figure 1). Axillary and pubic hair was absent. Her external genitalia were normal for her puberty stage, corresponding to Tanner stage 1 (Figure 2). Her weight was within the 85th-97th percentile for her age, and her length was below the 50th percentile for her age. There were no unusual skin pigmentations or gross limb or bone deformity. The rest of her physical examination is non-contributory.

The patient was admitted in our institution for further evaluation and monitoring. A repeat ultrasound was done, detailing the bilateral cystic ovarian masses, which have an aggregate volume of roughly 137cc and a Sassone score of 6 (Figure 3). The endometrium is intact and hyperechoic, and the uterus appears normal (Figure 4). Hormonal analysis revealed an elevated level of estradiol (167.96 pg/ml, normal postmenopausal <82), with depressed values of FSH (0.01 mIU/ml, normal postmenopausal 30-135) and LH (0.01 mIU/ml, normal postmenopausal: 13-80). Prolactin and β hCG were within normal levels for age. Tumor marker results revealed slightly elevated levels of CA 125 (36.5 U/ml, normal 0-35) and LDH (733 v/L, normal 313-618) and normal values of AFP (1.16 ng/ml, normal 0-15) and HE4 (47.1 pmol/L, normal postmenopausal <140). The patient's bone age was comparable to that of a 2 year old female based on Greulich-Pyle scoring, but this result is statistically insignificant (SD=1.8). An MRI of the brain also revealed no abnormal masses or lesions.

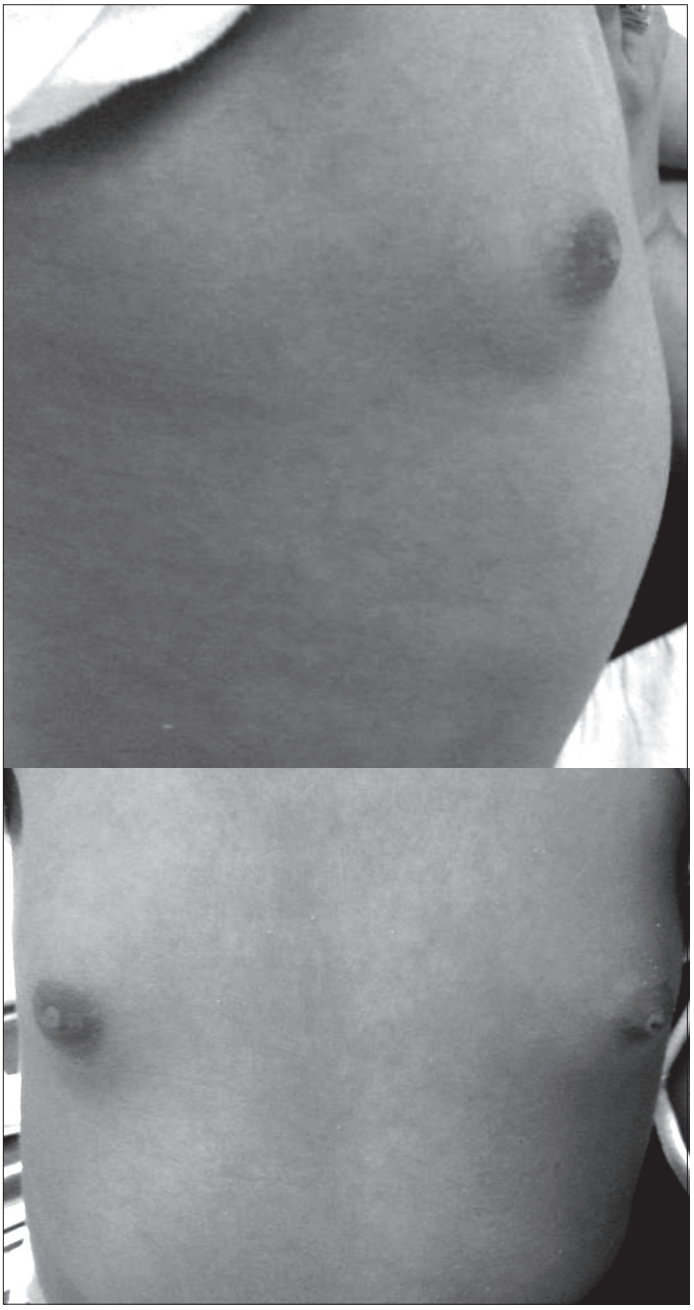

Figure 1. Anterior and lateral views of patient's chest, detailing the precocious breast development corresponding to Tanner stage 3.

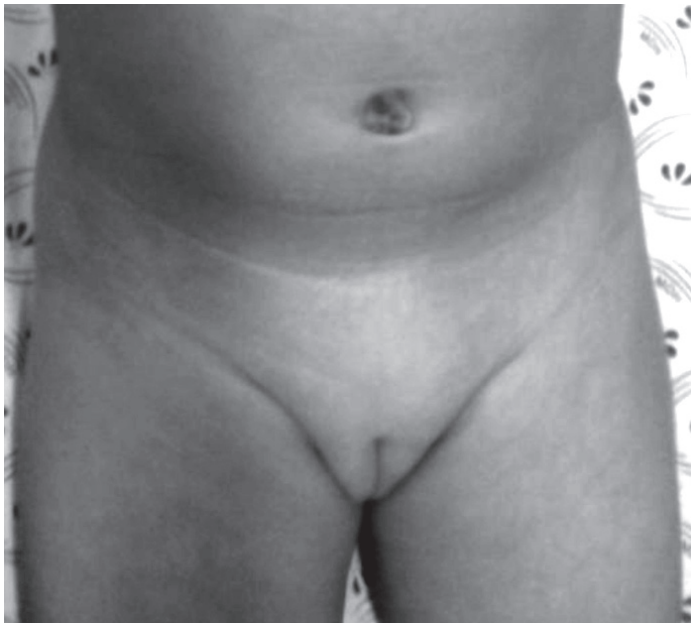

Figure 2. Anterior and lateral views of patient's groin, corresponding to Tanner stage 1

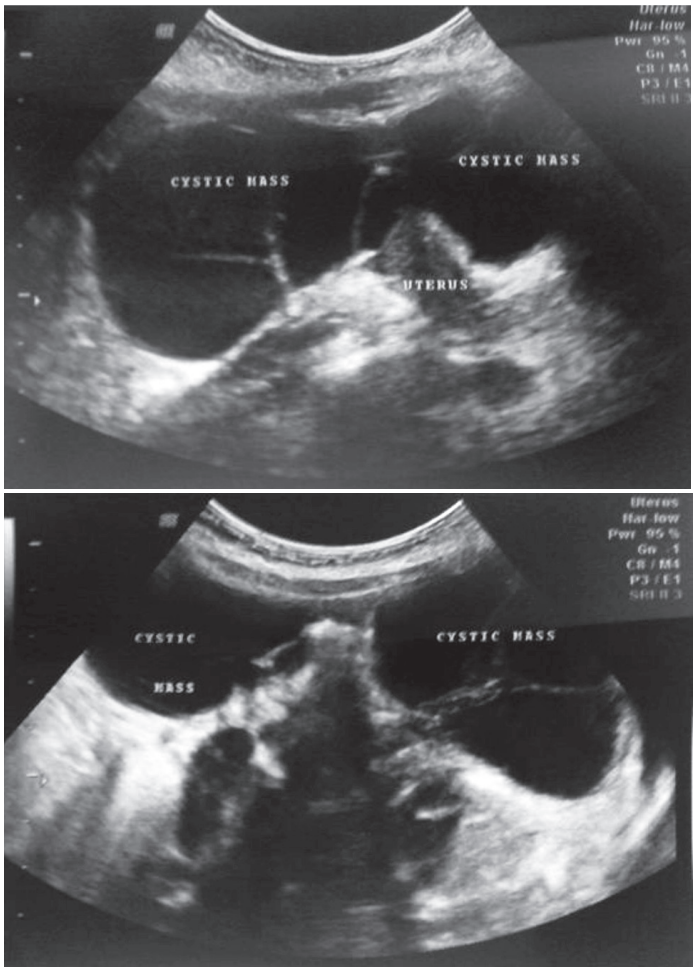

Figure 3. Pelvic ultrasound shows two cystic masses located anterior and superior to the uterus with Cyst 1: unilocular, thin-walled, anechoic, measuring 6.31 x 6.47 x 5.76cm (volume 123.15 cc) and Cyst 2: multilocular (3), Thick walled (0.33 cm), multi-septated (0.16 cm, thin), anechoic, measuring 7.19 x 6.08 x 4.96 cm (volume 113.58 cc). Sassone score of 6.

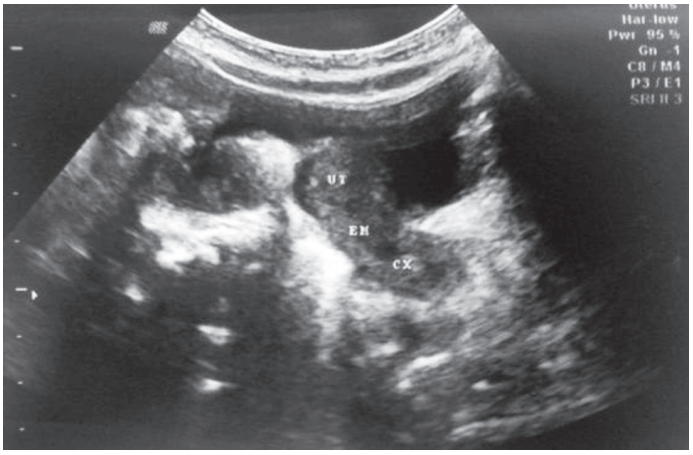

Figure 4. Pelvic ultrasound shows a normal sized for age, retroverted uterus an and intact hyperechoic endometrium.

Based on the laboratory and imaging results, the patient was diagnosed as a case of peripheral precocious puberty, secondary to autonomous, functional ovarian cysts. Vaginal bleeding was observed during her admission, and brownish streaks on her diaper were noted to persist up to the 3rd hospital day. Bleeding abated on the 4th hospital and she was subsequently sent home the following day.

DISCUSSION

Approach to diagnosis

The evaluation of a child suspected to have precocious puberty begins with a thorough history and physical examination, in order to determine the progression of pubertal development. The onset and timing of the development of secondary sexual characteristics may provide a diagnostic clue in determining the etiology of precocious puberty.

In the case described, breast budding preceded the onset of vaginal bleeding by about 4 weeks. While breast budding is indeed the first sign of normal puberty, there should be an interval of about 2 years before the onset of menarche (Fritz et al, 2011). Therefore, the patient's precocity does not recapitulate normal puberty, which is suggestive of a peripheral, rather than central, etiology. A previous study concluded that if a girl with precocious breast development progresses to vaginal bleeding within one year, then she is more likely to have ovarian disease, which is the most common cause for peripheral precocious puberty in girls (Hill et al, 1989). Also, since the secondary sexual characteristics noted

are feminizing, which in this case is isosexual since the patient is female, several etiologies for precocious puberty may already be excluded, such as ovarian arrhenoblastoma.

Another important consideration is the rate of progression of pubertal development. Height velocity (in cm/year) typically rises earlier in patients with precocious puberty, and can be a useful diagnostic clue (Papadimitriou et al, 2006). Thus, long term follow-up for growth rate monitoring is indicated for this patient. Skeletal maturation, measured as bone age, is also typically advanced in patients with precocious puberty. More importantly, an advanced bone age is more suggestive of a progressive precocity rather than a non-progressive, incomplete precocity such as premature thelarche. In this patient, bone age with reference to Greulich-Pyle grading is slightly advanced for age, but the difference with chronological age is not statistically significant. This however does not preclude the necessity of further evaluation, especially if pubertal development continues to progress in the immediate future.

Further laboratory evaluation is needed to confirm a diagnosis of precocious puberty based on history and physical examination. In particular, hormonal and imaging studies can help identify the etiology of the precocity, whether treatment is necessary and what mode of treatment is indicated. The first step is to confirm whether the etiology of the precocity is peripheral rather than central, and currently, a GnRH stimulation test is the gold standard for correctly diagnosing children with precocious puberty (Chae and Rheu, 2013). After administration of GnRH or an agonist like leuprolide acetate, LH (and FSH) concentrations remain low in peripheral precocious puberty, but are increased in central precocious puberty (Chae and Rheu, 2013). If basal levels of LH are markedly elevated (more than 5 mIU/mL, then a diagnosis of central precocious puberty can be made without proceeding to a GnRH stimulation test. However, patients with low or intermediate basal levels of LH should have a GnRH stimulation test to clarify the diagnosis (Carel et al, 2009).

In the case described, the basal LH levels are particularly low; along with an elevation in serum estradiol, this finding is highly suggestive of peripheral precocious puberty. At present, a GnRH stimulation test is yet to be done.

Imaging studies and further laboratory examinations are used to elucidate the etiology of precocity once the distinction between central and peripheral precocious puberty has been made by hormonal studies. Although a GnRH test has not yet been done, several considerations from the case make the diagnosis of peripheral precocious puberty highly likely. First, as discussed earlier, the timing of pubertal development does not recapitulate normal puberty, as one would expect from central precocious puberty. Second, a non-routine cranial MRI done on the patient revealed no CNS anomalies, and the normal serum prolactin excludes some pituitary tumors which may cause precocity; unfortunately, these findings do not exclude idiopathic causes of central precocious puberty. Lastly, and most importantly, pelvic ultrasound done initially revealed the presence of ovarian cysts, which is the most common cause of peripheral precocious puberty. The large size of the cysts is also consistent autonomous estrogenic function, as a diameter ≥9 mm is a strong indicator of autonomous ovarian activation (Rodriguez-Macias et al, 1999).

Pelvic ultrasound is typically used to reveal ovarian lesions that may cause peripheral precocious puberty, but uterine changes secondary to estrogen exposure can also be used as an index of progressive puberty; a uterine volume greater than 2.0 ml has been reported to have 89% sensitivity and specificity for precocious puberty (De Vries et al, 2006).

Other tests to confirm the peripheral cause of precocious puberty in this case include sex hormone levels (i.e. estradiol), and tumor markers such as B-hCG, LDH, and CA-125. Since the precocity is feminizing rather than virilizing, as confirmed by the elevated estradiol levels, tests for cause for hyperandrogenism such as cortisol, DHEA, DHEAS, and 17-hydroxyprogesterone are unnecessary. The negative results in the tumor markers provide more evidence that the etiology of this patient's condition is indeed a functional cystic ovarian lesion that causes hyperestrogenism, which in turn leads to the development of secondary sexual characteristics at a much earlier age than normal.

McCune-Albright syndrome should also be considered as a possible diagnosis when evaluating patients with peripheral precocious puberty. This rare disorder is caused by a G protein mutation that leads to continued stimulation of endocrine function,

and is characterized by a clinical triad of peripheral precocious puberty, café-au-lait skin pigmentation, and polyostotic fibrous dysplasia. In this case, the absence of the characteristic skin lesions and the normal radiographic findings render the triad incomplete, but at this point, one cannot completely rule out this disorder. In an eight-year longitudinal study of seven girls with precocious pseudopuberty secondary to ovarian cysts, the clinical symptoms of McCune-Albright syndrome became apparent only after 18-40 months after the initial diagnosis of precocious puberty (Rodriguez-Macias et al, 1999).

Approach to management

The management of peripheral precocious puberty is directed at the underlying pathology. Unlike central precocious puberty, this condition does not respond to medical treatment with GnRH agonists. Autonomous functional ovarian cysts, such as those in this patient, usually regress spontaneously within 2 – 3 months; hence conservative management is favored and surgical management is deferred as long as possible to avoid the risk of repeat surgery (Lee and Kerrigan, 2004). A recent study concluded that surgical drainage may be indicated in large ovarian cysts greater than 75cc in volume due to the much higher risk of ovarian torsion.

Prolonged exposure to elevated estrogen levels in peripheral precocious puberty may eventually lead to a secondary, central precocious puberty, due to the maturation of the GnRH pulse generator in the hypothalamus. Therefore, it has been proposed that surgery is indicated for functional ovarian cysts that persist for more than 3 months (De Sousa et al, 2008).

Pharmacologic antagonism of estrogen by means of aromatase inhibitors (Feuillan et al, 2007) and selective estrogen-receptor modulators (Eugster et al, 2003) may counteract the effects of hyperestrogenism in peripheral precocious puberty, but these treatments are usually reserved for more serious conditions such as McCune-Albright syndrome.

For this patient, a repeat pelvic ultrasound within 4 – 8 weeks is indicated to monitor for regression of the ovarian cysts; if the cysts have not resolved and the ultrasonic characteristics are still reassuring, then continued observation is appropriate as long as there is no progression of pubertal development or there are no symptoms of ovarian torsion.

SUMMARY AND CONCLUSION

In the case described, advanced breast development, soon followed by vaginal bleeding in an 18 month old female, with an elevated estradiol level, normal bone age and ultrasonographic findings of ovarian cysts, all suggest a diagnosis of peripheral precocious puberty, likely due to an autonomous functional ovarian cyst. Hormonal analysis is needed to distinguish between central and peripheral precocious puberty, and the low LH level of this patient is consistent with peripheral precocious puberty. Nevertheless, GnRH stimulation test is still considered the gold standard for identifying the cause of the precocious puberty. Autonomous functional ovarian cysts are the most common cause of peripheral precocious puberty, and the normal values for the various tumor markers requested are consistent with this diagnosis. Since these ovarian cysts typically regress within 2 – 3 months, a conservative management is favored; surgery is only reserved if there are signs of ovarian torsion on follow-up, or if pubertal development persists for more than 3 months. The progression of pubertal development or the recurrence of functional ovarian cysts is suggestive of McCune-Albright syndrome; this rare disorder cannot be immediately excluded on initial evaluation and may present only in later follow-ups.

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