Case report

Precocious menarche in a 9 years old girl due to autonomous ovarian cyst treated with letrozole.

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ABSTRACT

Background: Peripheral precocious puberty (PPP) is defined as the early pubertal maturation independent of gonadotropin stimulation. Autonomous ovarian cysts can be a cause of PPP or isolated precocious menarche. The differential diagnosis of ovarian cysts is important because of distinct management options.

Case presentaion: A 9 7/12-year-old girl presented because of rapid evolution of breast development and premature menarche. Estrogen levels were elevated while GnRH stimulation test revealed a blunt response. Pelvic sonogram demonstrated an ovarian cyst. She was started on oral letrozole. There was no further episode of menstruation. The cyst resolved spontaneously after three months.

Conclusion: Functional ovarian cysts usually regress spontaneously. This case highlights the effectiveness of letrozole therapy in promptly decreasing estrogen levels and immediately controlling menstrual bleeding.

Key Words: *pubertal development;precocious puberty;precocious menarche;ovarian cyst;letrozole*

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Introduction

Puberty is characterized by a series of maturational events leading to the attainment of adult reproductive capacity [1]. The definition of precocious puberty is the appearance of secondary sex characteristics before the age of 8 years in girls and 9.5 years in boys [1]. The incidence of precocious puberty is estimated between 1:5000 and 1:10000, with prevalence 10 times higher in girls [1, 2]. Isolated premature menarche is the apparition of menstrual like bleeding in prepubertal girls in the absence of secondary sex characteristics, usually before the age of 10 [1, 3, 4].

Small ovarian cysts are commonly seen in prepubertal children and are clinically insignificant [2]. Autonomous ovarian cysts are usually benign single cysts that function autonomously and produce estrogens [2]. They can lead to peripheral precocious puberty (PPP) or isolated metrorrhagia with inconsistent response to the gonadotropin releasing hormone (GnRH) test [1-3]. Autonomous ovarian cysts may develop at any age, but their mechanism of production is unknown [2]. They usually regress spontaneously after a few weeks or months, yet they have an important chance of recurrence [2].

The aim of this paper is to report a case of rapidly evolving puberty and premature menarche in a nine-and-a-half-year-old girl that turned to be secondary to a functional ovarian cyst that was managed with oral letrozole.

Case Presentation

A 9 7/12-year-old girl was referred to the endocrine department because of breast development that was noticed 2 months earlier and vaginal bleeding that occurred in the last 24 hours. She was born prematurely at 35 weeks of gestation and at the age of 7 years, she presented with idiopathic premature pubarche (pubic hair: Tanner 2) for which she was followed in the endocrine department every 6 months. The hormonal evaluation at the initial exam was within normal range and her bone age was 7 10/12. Two months prior to the symptomatology her hormonal profile was prepubertal (Table 1).

Her family medical history was unremarkable except for a history of polycystic ovary syndrome (PCOS) for her mother.

At the time she presented after menarche, her clinical examination revealed signs of breast development (Tanner 2- 3), axillary hair (Tanner 2) and pubic hair (Tanner 2- 3). Her external genitalia and clitoris were normal. Her weight and height measured in the 75th-90th percentile and 50th- 75th percentile, respectively, without an accelerated height velocity (Fig 1).

No signs of McCune-Albright syndrome (MAS), including café-au-lait skin pigmentation and bone deformity were identified on physical examination. Systemic examination was normal. The patient's bone age was 10 years and 6 months and the basal estradiol level was 2021.69 pg/ml (normal < 10 pg/ml), testosterone level was 45.4 ng/dl (normal < 0.1 ng/dl) and 17 OHP was 2.08 ng/ml (normal 0.5-2 ng/ml). The initial ultrasonographic study of the patient's abdomen and pelvis revealed a simple cyst of the left ovary measuring 5.63 × 4.09 x 4.67 cm. The uterus was enlarged with a length of 6.24 cm (normal ≤ 3 cm -Fig 2).

Hormonal analysis revealed suppressed baseline LH and FSH levels (LH <0.10 mIU/ml [during puberty > 0.5], FSH, 0.23 mIU/ml [during puberty > 4]). Serum gonadotropin responses to GnRH stimulation were suppressed. TSH, prolactin, beta human chorionic gonadotropin (β-HCG), and alpha fetoprotein (AFP) were all within normal range. We administered oral letrozole, at a dose of 2.5mg per day, once daily. Treatment was well tolerated and was continued for 3 months. Two months later, the patient remained asymptomatic, and there was no other episode of vaginal bleeding. Hormonal analysis demonstrated a decrease in estradiol levels that became undetectable (< 5 pg/ml). FSH baseline level was 5.35 mIU/ml and LH 0.18 mIU/ml. On ultrasound, the ovarian cyst completely regressed. Therapy was discontinued and there was no relapse of the cyst. One year later, at the age of 10 9/12 years, puberty was evolving normally (breast development: Tanner 3, axillary hair: Tanner 2-3 and pubic hair: Tanner 3). Letrozole was helpful in decreasing estrogen levels faster and possibly preventing another menstrual cycle and bone maturation. The natural history of simple ovarian cysts is spontaneous regression but the use of an aromatase inhibitor may decrease the number of menstrual cycles prior to cyst resolution and thus eliminate psychological stress and prevent bone maturation.

Discussion

Precocious puberty can be classified as central (or true), when there is early activation of pulsatile GnRH secretion and peripheral (or pseudopuberty), which is GnRH independent [1, 2]. The vast majority of cases with precocious puberty are because of central precocious puberty (CPP) and a small percentage is due to PPP [1]. PPP is caused by the peripheral production of sex steroids independent of gonadotropin stimulation [1].

Table: Laboratory data of the patient

	Two months prior to diagnosis	At Diagnosis	Normal Range
FSH (mIU/ml)	3.38	0.23	Tanner II: 0.5-7
LH (mIU/ml)	0.1	<0.1	Tanner II: <4
Testosterone (ng/dl)	0.14	45.4	Tanner II <0.3
Estradiol (pg/ml)	9.22	2021.69	<10
DHEA-S (mg/dl)	110.5	103	95-1360
Prolactin (ng/ml)	11.6		2-25
TSH (mIU/ml)	6.16	1.85	0.66-4.9
FT4 (ng/dl)	0.86	1.11	1-1.7
17 OHP (ng/ml)		2.08	Tanner I/II: 0.5-2

FSH: Follicle stimulating hormone; LH: Luteinizing hormone; DHEA-S: Dehydroepiandrosterone sulfate; TSH: Thyroid-stimulating hormone; FT4: Free thyroxin; 17 OHP: 17-hydroxyprogesterone

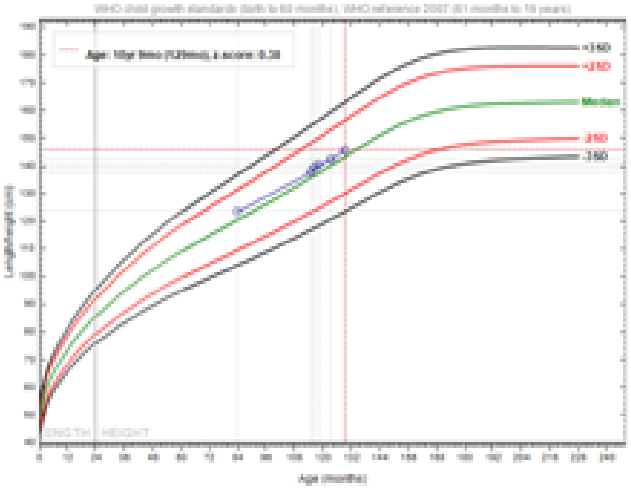

Figure 1: Growth chart of the patient

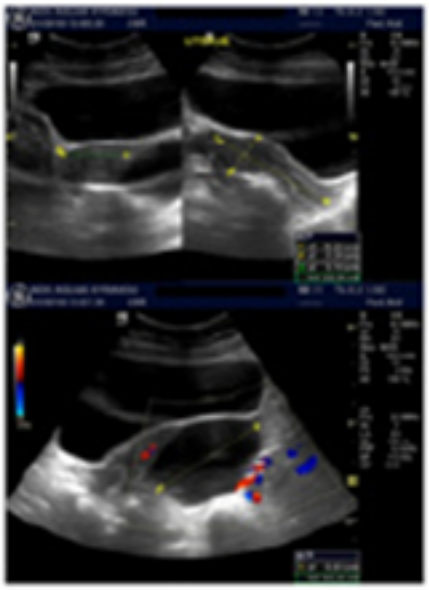

Figure 2: Pelvic ultrasound a. Uterus; b. Ovarian cyst

Symptomatology can range from breast enlargement, axillary and pubic hair development, changes of external genitalia, vaginal discharge or even bleeding [1, 3]. In normal puberty, uterine bleeding usually occurs at breast Tanner stage 3-4, 2-2.5 years after the first sign of breast enlargement [3]. A discordant pubertal development suggests peripheral causes of precocious puberty such as ovarian follicular cysts, MAS, estrogen secreting ovarian or adrenal tumors and exposure to estrogenic endocrine disrupting chemicals or contact with estrogen containing creams [1, 3].

Autonomous ovarian cysts produce estrogens independently of GnRH stimulation and may lead to PPP [2]. Possible consequences of a functional ovarian cyst are the acceleration of growth and skeletal maturation leading to premature epiphyseal closure and a decrease of final adult height [1]. The diagnosis of PPP due to an autonomous ovarian cyst will demand a careful and detailed history and clinical examination of the patient, laboratory exams with tumor markers and imaging [1]. The hormonal profile usually consists of elevated estrogen levels with low or undetectable basal levels of FSH and LH [1]. A GnRH stimulation test will show a prepubertal or even suppressed response [1, 3]. This test will help us differentiate PPP from CPP leading to a different therapeutic management.

Radiological investigation with a left hand x ray and a pelvic ultrasound will provide useful information for the differential diagnosis [1]. Diagnosis of functional ovarian cysts is done with a pelvic ultrasound showing one or more large, unilateral, or bilateral ovarian cyst [2]. According to bibliography an ovarian cyst associated with precocious puberty is generally larger than 20 mm [2].

MAS is a rare cause of PPP caused by post zygotic somatic activating mutations in the GNAS1 gene [5, 6]. Classic triad of MAS is precocious puberty, fibrous dysplasia of bones and café au lait macules with irregular borders (coast of Maine) [5]. Other endocrine manifestations are GH excess, hypercortisolemia, hyperprolactinemia,hyperthyroidism,andhypophosphatemia [1, 5]. Girls with MAS sometimes present with autonomous functional ovarian cysts [5, 7].

Gonadal and adrenal tumors are infrequent causes of PPP [1]. Different subtypes associated with endocrine manifestations are germ cell tumors, sex cord stromal cell tumors and adrenocortical tumors [5]. B-HCG and AFP levels may be elevated in gonadal tumors [5]. When completely surgically resected, they have an excellent prognosis [5].

Management of autonomous ovarian cysts in prepubertal girls can be conservative or surgical [2, 7]. A simple follow up is preferred as the first choice, as most cysts will regress spontaneously, and pubertal signs will also regress [2, 8, 9]. If they persist beyond 4- 6 weeks or present recurrences, a medical treatment with third generation aromatase inhibitors (anastrozole, letrozole) daily is suggested [5]. Other pharmacological agents used in girls with MAS are cryproterone acetate (antiandrogen), tamoxifen (estrogen receptor modulator) and fulvestrant (estrogen receptor antagonist) [5, 7]. According to the literature, there is an important chance of recurrence [2, 8, 9]. Surgical removal of cysts is indicated in cases of torsion or hemorrhage or where there is an increased suspicion for malignancy [2, 8, 9].

In a review of the literature by Papanikolaou et al, most cases of autonomous ovarian cysts with a simple follow up regressed spontaneously (11 out of 13), within a period of six weeks. Nine of thirteen girls managed conservatively presented with recurrences within a median time of 13.5 months. Three out of twenty six cases progressed to CPP [2].

In conclusion, the patient did not present with premature puberty but rather with a rapidly evolving puberty which progressed to premature menarche as early as 2 months after thelarche. Precocious puberty is usually of central origin, but in the differential diagnosis peripheral causes, like ovarian cysts, should always be considered. The patient will need a prolonged follow up during her puberty.

Abbreviations

17 OHP: 17-hydroxyprogesterone
AFP: Alpha fetoprotein
B- HCG: Beta human chorionic gonadotropin
CPP: Central precocious puberty
DHEA-S: Dehydroepiandrosterone sulfate
FSH: Follicle stimulating hormone
GnRH: Gonadotropin- releasing hormone
LH: Luteinizing hormone
MAS: McCune-Albright syndrome
PCOS: polycystic ovary syndrome
PPP: Peripheral precocious puberty
TSH: Thyroid-stimulating hormone

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