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Precocious puberty in a healthy 2 years old girl: Ovarian Sertoli-Leydig cells cancer

Jennifer Monroy [b], Carolina Jaramillo [b], Sasha González [a,*]

[a] Pediatrician, North University, Barranquilla, Colombia
[b] Pediatric Endocrinologist. Pablo Tobón Uribe Hospital, Medellín, Colombia

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ABSTRACT

Precocious puberty refers to appearance of secondary sexual characteristics, increased growth rate and reproductive capacity before 8 years in girls, and 9 years in boys. The etiology can be diverse, either central activation of hypothalamus-pituitary gonadal axis or by endogenous production or exogenous administration of sex steroids. Peripheral precocious puberty is less common and Leydig-Sertoli cell tumors comprise 1–2% of the pediatric ovarian malignancies. (1) These tumors commonly present in the second or third decade of life but can present as early as 2-years of age.(2).

We describe a case of precocious puberty caused by ovarian Sertoli-Leydig cancer in a young girl with no pre-existing medical issues. The 2-year-old patient was referred from Saint Martin to the Pediatric endocrinology for evaluation of pubic hair and breast development which started 3-month prior to presentation. On exam, the patient was noted to have abdominal prominence which prompted obtaining abdominal imaging which showed an ovarian tumor which was subsequently removed.

1. Introduction

Sex cord stromal tumors include Sertoli-Leydig cell tumors (SLCTs) which account for 1% of pediatric ovarian cancers [1]. Elevated testosterone or androstenedione could be suggestive SLCTs. Pathogenic germline DICER1 is associated to SLCTs, lung, kidney, thyroid (as multinodular goiter), ophthalmologic, otolaryngologic, central nervous system tumors and gastrointestinal polyps. DICER1 related diseases are autosomasl-dominant, 80% of DICER1 mutations are inherited from family. This variants increase risk of neoplasms at early childhood, unlike adults [3].([4]). Approximately 29% of non-epithelial ovarian tumors could carry a DICER1 mutation, if only SLCTs is taken into account, it reaches 60% [5].

Patients with peripheral precocious puberty present isosexual physical changes (consistent with birth sex) or heterosexual physical changes (contrary to birth sex), according to hormonal abnormalities. Based on clinical data obtained from 44 patients ranging in age from 6 months to 17-years of age, abdominal pain and virilization are the main presenting features [6].

The rare occurrence of these tumors poses a challenge a timely diagnosis. Only six cases of SLCTs have been reported under age of eight years in the literature so far [7].([8]) [9]([10]) [11]. Prognosis of ovarian SLCTs is correlated with degree of tumor grading and staging according to FIGO (International Federation of Gynecology and Obstetrics) [1].

Here we present a case of a 2-year-old girl who was referred to the Pediatric endocrinology service for evaluation of precocious puberty.

2. Case presentation

A 2-year-old African-American girl with no medical relevant history, was referred from Saint Martin to the Pediatric endocrinology for evaluation of pubic hair and breast development which started 3-month prior to presentation.

On exam, the patient was noted to have abdominal prominence, palpable liver 7 cm below costal margin, palpable breast buds, pubic hair filling the entire triangle and clitoromegaly.

Initial tests showed elevated estradiol 87pg/ml (prepuberal <15pg/ml) and total testosterone 583,6ng/dl (<3,4ng/dl) slight elevation of AST 261 UI/L (<60UI/L) and ALT 273UI/L (<30U/I) and hypothalamus-pituitary-gonadal axis was suppressed LH 0.0 mIU/ml (0.02–0.18mIU/ml). The abdominal ultrasound showed a well-defined,

* Corresponding author.
E-mail addresses: Sashago90@gmail.com, sashatupediatra@gmail.com (S. González).

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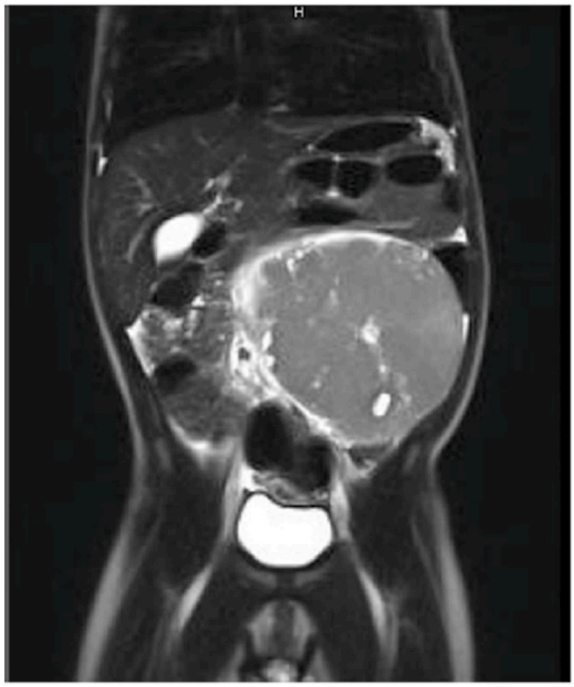

Fig. 1. Initial contrast MRI. The coronal image shows a well-defined 11.2 × 12.0x2c.4 cm tumor of the right ovary.

hypoechoic, vascular mass measuring 11.2 × 7.6 × 9.9cm, located in mesogastrium. To better characterize the mass, MRI of the abdomen/pelvis was obtained which showed a cystic intraperitoneal tumor measuring 11.2 × 12.0 × 2.4 cm in the left hemiabdomen originating from the right ovary without thoracic or bone involvement (Fig. 1).

Patient was diagnosed with peripheral precocious puberty secondary to ovarian tumor. In consensus with oncology, right salpingo-oophorectomy was performed (Fig. 2). The pathology report was consistent with a poorly differentiated Sertoli-Leydig tumor without extracapsular extension or lympho-vascular invasion. The tumors mitotic index was two mitoses per 10 high-power fields (see Fig. 3).

One week later the hormonal profile return to normal values, estradiol <10pg/ml and total testosterone <3.4ng/dl. Genetics reports karyotype 46,XX; and variant of uncertain meaning c.4537G > A in ALK (predisposition to neuroblastoma), variant of uncertain meaning c.1934T > C In SDHA (predisposition to paraganglioma, pheochromocytoma, gastric tumors and deficiency in type II mitochondrial complex). No DICER1 mutation was found. After three years of follow-up thelarche and clitoromegaly regressed; pubic hair become thinner and straighter, accelerated growth speed 9.9cm/year persist during the first year of diagnosis. Follow-up was every 3 months using hormonal profile and imaging, during the last 2 years without change. No tumor recurrences or lung-bone involvement has appeared.

3. Discussion

SLCTs belong to sex cord tumors, a subgroup of ovarian tumors. They are very rare, corresponding to 0.5% of ovarian tumors and 1% of sex cord tumors [12].

Sertoli-Leydig cell tumors usually present in the second and third decades of life [2]. This patient is the second youngest patient reported in the literature worldwide and the first reported in Colombia. The marked appearance of pubic hair, thelarche, and clitoromegaly at such early age led us to suspect a peripheral etiology for the patient's precocious puberty. Based on patient's abdominal exam finding the initial imaging studies included abdominal US and MRI of the abdomen/pelvis which showed a large ovarian mass. Given the imaging showed the mass was confined to the ovary, the decision to proceed with unilateral salpingo-oophorectomy was made. The tumor was found with an intact capsule, surface compromise for a FIGO Ic classification. Thanks to its benign course and early detection, chemotherapy was not indicated. Immunohistochemistry was positive for inhibin and calretinin which was consistent with the SLCT diagnosis and excluded other epithelial tumors.

What makes this case unique is the young age at presentation and lack of clinical symptoms such local compressive symptoms including abdominal pain. However, the marked physical findings allowed a quick diagnosis impression. The survival rate is 92.3% for stage 1 and

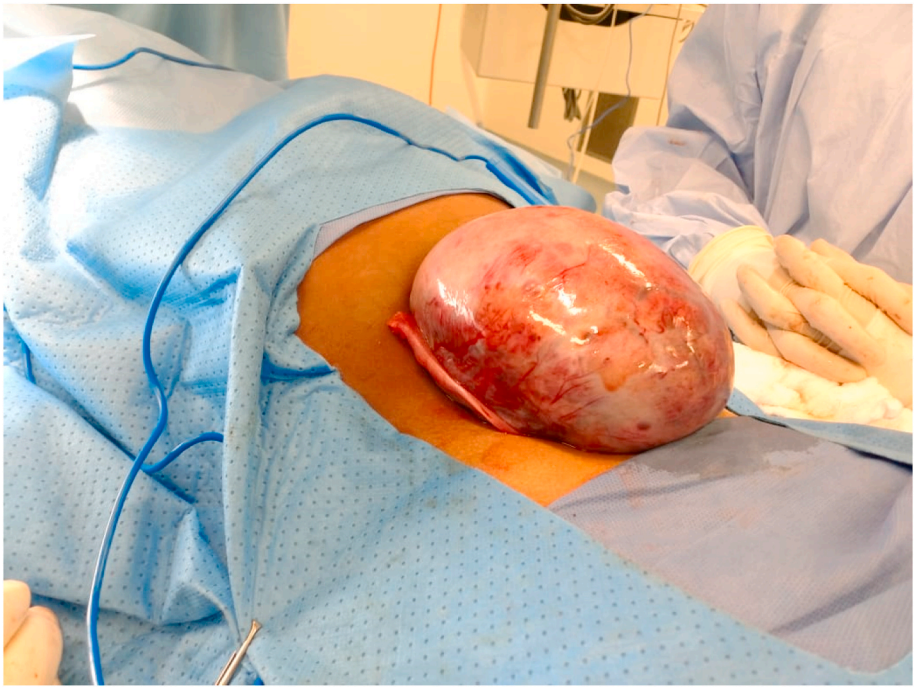

Fig. 2. Sertoli-Leydig cells tumor before resection in operating room.

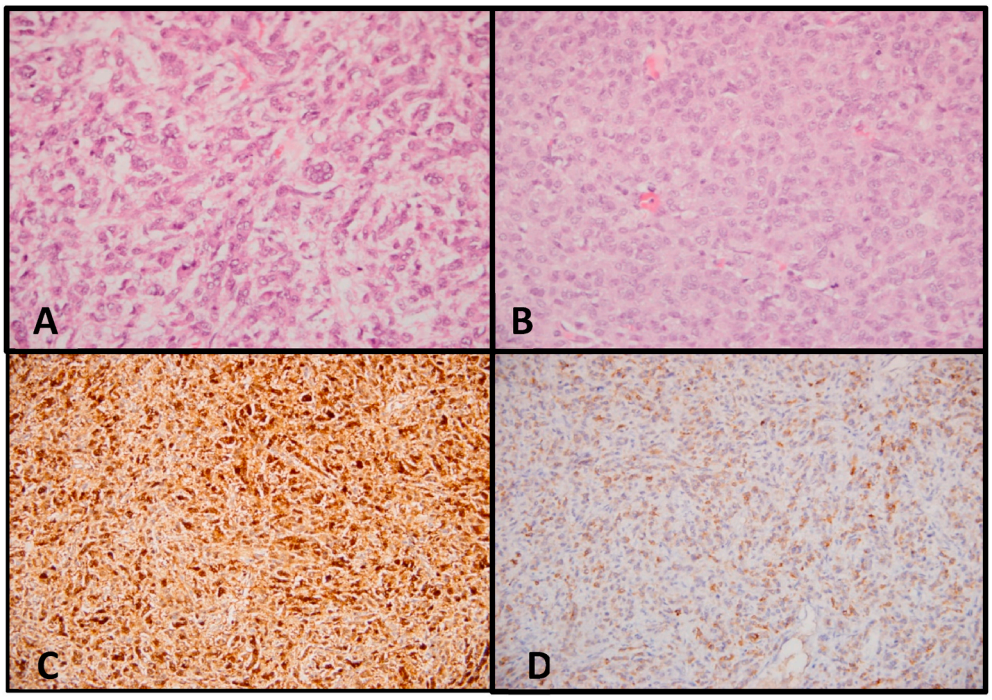

Fig. 3. Sertoli-Leydig cell tumor. A. Poorly differentiated Sertoli cells with poorly differentiated tubules and bizarre cells. B Leydig cell conglomerates with abundant eosinophilic cytoplasm. C neoplastic cells express calretinin and inhibin (D). Heterologous elements are not observed.

recurrence is low [12]. Follow-up was decided every 3 months using hormonal profile and RMN/US, during the first two years after surgery without alteration.

SLCTs are considered to be tumors of unknown malignant potential. Malignant potential is zero in the well differentiated tumor, about 11% in the intermediate type, 59% in poorly differentiated and 19% in tumors with heterogenous elements [13].([14]).

In older women, removal of uterus, ovaries, omentum are considered to be standard procedures. But at an early age we must preserve her hormonal axis and reproductive capacity [15].

According to the current literature, three or four periods of adjuvant chemotherapy with PEB (cisplatin, etoposide and bleomycin) or PAC (cisplatin, dactinomycin and cyclophosphamide) are recommended in intermediate or poorly differentiated tumors, or in patients with advanced stage diseases [16].

4. Conclusion

This patient shows a particular behavior of an infrequent type of ovarian tumor. The rare occurrence of these tumors poses a challenge for timely diagnosis. A benign prognosis is associated with an early stage detection. In this case, tumor removal was the only treatment required.

The main concern are patients without related signs or symptoms, reaching 25% of a large series of cases [17]. A clear protocol is not yet available, but sharing the experiences of experts helps guide these types of rare conditions.

Conflicts of interest/financial disclosures

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Declaration of competing interest

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