

Paul R. D'Alessandro, MD, MSc, Jillian Hamilton, MBChB, Karine Khatchadourian, MD, MSc, Ewa Lunaczek-Motyka, MD, Kirk R. Schultz, MD, Daniel Metzger, MD, Rebecca J. Deyell, MD, MHSc

# Precocious puberty: A red flag for malignancy in childhood

Three clinical cases of precocious puberty resulting from rare but serious functional solid tumors in children highlight the need for physicians to identify the condition early and refer to tertiary care to minimize morbidity and optimize survival.

*Dr D'Alessandro is a pediatric hematology/oncology subspecialty resident in the Division of Pediatric Hematology, Oncology, and Bone Marrow Transplant, Department of Pediatrics, University of British Columbia, British Columbia Children's Hospital Research Institute.*

*Dr Hamilton is a general practice specialty trainee, NHS Forth Valley, Larbert, United Kingdom. Dr Khatchadourian is a pediatric endocrinologist in the Division of Endocrinology, Department of Pediatrics, University of Ottawa, Children's Hospital of Eastern Ontario. Dr Lunaczek-Motyka is a pediatric hematologist/oncologist in the Department of Pediatrics, University of Victoria, Victoria General Hospital.*

*Dr Schultz is a pediatric hematologist/oncologist in the Division of Pediatric Hematology, Oncology, and Bone Marrow Transplant, Department of Pediatrics, University of British Columbia, BC Children's Hospital Research Institute. Dr Metzger is a pediatric endocrinologist in the Division of Endocrinology, Department of Pediatrics, University of British Columbia, BC Children's Hospital Research Institute. Dr Deyell is a pediatric hematologist/oncologist in the Division of Pediatric Hematology, Oncology, and Bone Marrow Transplant, Department of Pediatrics, University of British Columbia, BC Children's Hospital Research Institute.*

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**ABSTRACT:** Pediatric solid tumors have a range of clinical presentations, including those driven by the ectopic production of hormones secreted by some malignancies. Functional tumors lead to a variety of presentations, including Cushing syndrome, growth acceleration, abnormal virilization or feminization, and hypertension with electrolyte abnormalities. Precocious puberty, the onset of secondary sexual characteristics before age 8 in girls or 9 in boys, may be a warning sign of occult malignancy. Early referral is critical to optimize survival and limit disease- and treatment-related morbidities. Diagnostic workup and treatment should be guided by an interdisciplinary specialist team. Some tumors are associated with inherited cancer predisposition syndromes, which may have implications for surveillance and screening of family members. We describe a series of patients with rare functional tumors who presented with peripheral precocity to our tertiary referral centre at BC Children's Hospital to highlight key concepts for physicians: recognize, refer early, and review recommendations for genetic screening.

## Background

Functional solid tumors in childhood can arise from the adrenal glands, gonadal tissue, or extra-gonadal tissues. Although these tumors sometimes present with palpable testicular or abdominal masses, many do not. Functional tumors secrete hormones, leading to diverse presentations with Cushing syndrome, precocious puberty, abnormal virilization or feminization, and hypertension with electrolyte

abnormalities.<sup>1-3</sup> These tumors may present with early onset of isosexual or contrasexual puberty as a first symptom. Treatment may involve surgery, chemotherapy, and/or radiotherapy. Genetic testing or counseling may be indicated for families. Early identification minimizes disease-related morbidity and mortality and optimizes outcomes. We present illustrative cases of functional solid tumors in children from British Columbia with the aim of educating physicians about these rare but serious tumors.

## Case data

### Case 1

A previously healthy 12-year-old girl presented with a 3-year history of progressive virilization and Cushingoid features, including hoarse voice, hirsutism, central obesity, pubic and axillary hair, abdominal striae, interscapular fat pad, acanthosis nigricans, and a 6.8 kg weight gain. She was premenarchal. She had been evaluated by multiple clinicians over a period of 18 months, at which point she was assessed by a pediatrician who urgently referred her to our centre. At the time of consultation, her weight and BMI were > 99.9th percentiles, while her height was at the 20th percentile. There were no prior concerns with growth, development, or short stature. The patient's blood pressure was 122/63 (94th percentile systolic, 51st percentile diastolic). She was Tanner stage 3 for axillary and pubic hair and Tanner stage 2 for breast development. No lymphadenopathy, abdominal mass, hepatosplenomegaly, or clitoromegaly were identified.

Investigations revealed elevated serum cortisol (367 nmol/L; normal for age and time of day = 61 to 349 nmol/L) and total testosterone (2.8 nmol/L; normal for age = < 1 nmol/L) with normal electrolytes. Dehydroepiandrosterone sulfate (DHEAS) was normal. Low-dose and high-dose dexamethasone suppression tests failed to show suppression of serum and urinary cortisol. Bone age was advanced at 15 years. Abdominal ultrasound and subsequent MRI and fluorodeoxyglucose (FDG)-PET/CT revealed an FDG-avid left adrenal mass measuring 3.4 cm in maximal dimension, with no extension into adjacent structures or metastatic disease.

The patient underwent laparoscopic left adrenalectomy with perioperative stress-dose steroids. Pathology was consistent with adrenocortical adenoma with negative margins. The patient did not require adjuvant treatment. Surveillance imaging (abdominal MRI every 3 months for the first 6 months, and abdominal MRI or ultrasound annually until age 17) demonstrated no recurrence. Her symptoms resolved and she progressed with normal puberty. However, she had prolonged adrenal insufficiency. Her lack of adrenal recovery was unusual given that she had a remaining, presumably functional, adrenal gland. At the time of transition to adult care, her height was at the 14th percentile (-1.1 SD from mean) and her cortisol levels (at baseline and post-adrenocorticotropic hormone [ACTH] stimulation) remained low. Attempts to wean her off steroids were unsuccessful. At age 21, she remains on physiologic low-dose oral hydrocortisone replacement.

## Case 2

A 3-month-old infant presented to her general practitioner with secondary sexual characteristics and Cushingoid features, including hirsutism, acne, moon facies, interscapular fat pad, and body odor. She was referred to a pediatrician. While awaiting pediatric assessment, she re-presented at 6 months of age after developing new shortness of breath, orthopnea, and dyspnea while breastfeeding. The family was directed to hospital, where the child was determined to have signs of cardiac failure. Initial abdominal ultrasound revealed a left flank mass. The endocrinology service was contacted,

and the patient was transferred urgently to the pediatric ICU for stabilization. Notably, her paternal grandmother had separate cancers of the female reproductive tract at age 45 and 50 years. The paternal great-grandfather had passed away from colon cancer in his 70s.

Serum total testosterone was very high at 43.8 nmol/L (normal for age = < 0.6 nmol/L), DHEAS was elevated at 22.4  $\mu$ mol/L (normal for age = 0.2 to 1.8  $\mu$ mol/L), random cortisol was elevated at > 1600 nmol/L (normal for age and time of collection = 100 to 276 nmol/L), renin was elevated at 11.82 ng/L/s (normal for age = < 2.30 ng/L/s), and androstenedione was elevated at > 41.4 nmol/L (normal for age = 0.2 to 0.9 nmol/L). Electrolytes and aldosterone were normal (2170 pmol/L; normal for age = 135 to 2430 pmol/L). A chest X-ray demonstrated cardiomegaly, and an ECG demonstrated biventricular hypertrophy. An echocardiogram revealed septal hypertrophy with cardiomyopathy and decreased ejection fraction. Intermittent left ventricular outflow tract obstruction was noted due to the septal hypertrophy, secondary to chronic endogenous steroid excess. The patient remained unstable in the pediatric ICU, with two asystolic cardiac arrests followed by resuscitation and return of spontaneous circulation. A CT of the abdomen revealed a 7.0  $\times$  5.6  $\times$  7.7 cm heterogeneous mass arising from the left adrenal fossa, displacing the ipsilateral kidney. Thrombus was noted in the left renal vein extending into the inferior vena cava. A CT of the chest revealed three small, nonspecific nodular opacities (up to 3 mm in size) in the right upper and lower lung lobes.

The patient underwent laparotomy to obtain tissue diagnosis. In order to prevent tumor spillage, a left adrenalectomy and nephrectomy with inferior vena cava thrombectomy were performed. She experienced rebound hypertension postoperatively and was managed with a beta-blocker. The patient remained on glucocorticoid and mineralocorticoid replacement postoperatively for adrenal insufficiency. Pathology and histology were consistent with adrenocortical carcinoma with intravascular extension into the vena cava and extracapsular invasion. Following review by the multidisciplinary tumor board, the patient received modified adjuvant

chemotherapy in the setting of comorbidities. She received carboplatin rather than cisplatin to limit renal toxicity, and etoposide at 50% of the usual dose to limit myelosuppression. Doxorubicin was omitted due to cardiac toxicity risk. Daily oral mitotane was given. After two chemotherapy cycles, repeat PET-CT imaging demonstrated multiple new, small pulmonary nodules (2 to 4 mm in size). Due to concern about radiographic progression and improved clinical status, the patient was escalated to full dose cisplatin, etoposide, and doxorubicin in combination with daily oral mitotane as per the Children's Oncology Group ARAR0332 protocol.<sup>4</sup> She completed six additional cycles of chemotherapy and continued oral mitotane for a total of 18 months. Her major toxicities included mucositis requiring total parenteral nutrition, febrile neutropenia, and grade 3 (moderate to severe) bilateral sensorineural hearing loss with speech delay that required hearing aids. Pulmonary nodules were no longer present by the end of chemotherapy. Repeat echocardiogram demonstrated resolving cardiomyopathy with normalization of function (ejection fraction 63%). Ten months following initial diagnosis, secondary sexual characteristics improved clinically. Serum DHEAS and testosterone normalized within 3 to 6 months following surgery and six cycles of chemotherapy. The patient was referred to medical genetics. Family testing revealed germline TP53 tumor suppressor gene mutation (Li-Fraumeni syndrome) in the patient, her father, and paternal grandmother. The patient has two sisters, whom the family elected to test: they do not carry the TP53 variant. The patient has subsequently undergone screening per the Toronto protocol for early detection of other malignancies, including breast and thyroid cancer, leukemias, lymphomas, and sarcomas.<sup>5,6</sup> She remains well at age 9 with no recurrence, secondary malignancy, or new malignancy.

## Case 3

An 11-year-old boy presented after a noticeable growth spurt at age 8, followed by a development of a beard, axillary hair, acne, and body odor by age 9. His parents noted a plateau in his height velocity between age 10 and 11. He was seen by multiple care providers, including a pediatrician, over the course of 1 year

for advanced puberty and abdominal pain. The family was reassured that his puberty was within upper normal limits. On a subsequent visit, 5 days prior to referral to our centre, the patient disclosed an interval 3-month history of enlarging left testis. A testicular mass was palpable on examination, and scrotal ultrasound with Doppler demonstrated a  $3.1 \times 2.2 \times 1.7$  cm well-circumscribed, heterogenous mass in the left testis, with calcifications and associated varicocele. Time from symptom onset to referral was approximately 3 years; time from first physician assessment to referral was 1 year.

On physical examination, the patient's height was 161.6 cm (> 97th percentile), weight was 63.9 kg (> 97th percentile), and BMI was  $24.5 \text{ kg/m}^2$  (> 97th percentile). He had a full beard, deep voice, and axillary hair (Tanner stage 4–5), and asymmetric testes. The left testis was enlarged, nontender, and firm. Investigations were notable for elevated serum testosterone at  $26.3 \text{ nmol/L}$  (adult male range) and DHEAS at  $11.2 \text{ } \mu\text{mol/L}$  (upper normal adult male), with suppressed luteinizing hormone (LH) of  $< 0.2 \text{ IU/L}$  and low follicle-stimulating hormone (FSH) of  $< 0.7 \text{ IU/L}$ . Alpha-fetoprotein (AFP) was slightly elevated at  $8.9 \text{ } \mu\text{g/L}$  (normal  $< 8.4 \text{ } \mu\text{g/L}$ ). Beta-human chorionic gonadotropin ( $\beta\text{hCG}$ ) was undetectable. Bone age was advanced at 17 years. FDG-PET/CT was negative for metastatic disease in the chest, abdomen, and pelvis.

The patient underwent left radical orchiectomy with no complications. Pathology was consistent with a Stage I Leydig cell tumor with negative margins (T1N0M0). He was assessed in follow-up by our pediatric endocrinology service. Due to chronic exogenous androgen exposure, he would have limited skeletal growth potential, as growth plates were approaching fusion. He has subsequently shown evidence of reactivation of his central hypothalamic-pituitary-gonadal axis with normalization of serum LH and FSH. He remains well at age 13 with no evidence of recurrence; however, his height has plateaued, with a predicted final adult height around the third percentile.

## Discussion

In our series, patients presented with precocious puberty, in addition to signs of steroid excess

in those who had adrenal tumors. The first two cases highlight the continuum of functional adrenocortical tumors, from isolated, functional benign adenoma to metastatic adrenocortical carcinoma associated with Li–Fraumeni syndrome. The third case highlights a functional Leydig cell tumor, where precocious puberty predated identification of a testicular mass by several years. Adolescent patients may be hesitant to disclose signs of precocious puberty or testicular masses. Thorough history and physical examination are critical. Though not highlighted in this series, some central nervous system tumors, including ependymomas, optic gliomas, and astrocytomas, can also present with true isosexual central precocious puberty. These tumors are rare. In the first and third cases, patients experienced delays from the onset of symptoms to diagnosis and treatment. In the second case, the infant presented with life-threatening cardiac failure while awaiting pediatric assessment. All patients experienced short- and long-term morbidities, some of which are permanent.

## Background, epidemiology, and cancer predisposition

**Functional adrenocortical tumors:** Adrenocortical tumors comprise 0.2% of pediatric cancers, with an incidence of 0.7 to 2.0 cases per million in the general population.<sup>7,8</sup> There is a bimodal distribution, with peaks under age 10 and in the fourth decade.<sup>1,9</sup> In children, the median age is 3 to 4 years, with a second, smaller peak in adolescence.<sup>10</sup> Pediatric adrenocortical tumors exist on a spectrum from benign, incidental adenomas to aggressive, malignant carcinomas. Classically, adenomas are well defined, spherical, and small ( $< 2 \text{ cm}^3$ ). Carcinomas are typically larger, lobulated, and demonstrate hemorrhage and necrosis. The adrenal cortex is made up of three distinct layers: zona glomerulosa (mineralocorticoid production), fasciculata (glucocorticoid production), and reticularis (sex hormone production). Children are more likely to have isolated, functional tumors that present with symptoms; teenagers are more likely to have nonfunctional tumors that have metastatic spread at presentation.<sup>1</sup>

Pediatric adrenal tumors can be associated with inherited cancer predisposition syndromes, including Li–Fraumeni (germline TP53 tumor

suppressor gene), Beckwith–Wiedemann (alterations on chromosome 11p15 affecting imprinting of genes), multiple endocrine neoplasia type 1 (11q13 gene), familial adenomatous polyposis (with at least four associated genes), and Carney complex (PRKAR1A tumor suppressor gene causing cardiac and cutaneous myxomas and adrenal hyperplasia).<sup>11,12</sup>

**Functional sex cord-stromal tumors:** Testicular and ovarian tumors are very rare in childhood, accounting for 1% to 2% of all childhood tumors.<sup>13</sup> They can be classified into germ cell and non-germ cell tumors. Nongermline sex cord-stromal tumors can be functional and may secrete estrogen and/or testosterone. They may also present as a testicular mass or, in the case of an ovarian tumor, with abdominal pain, mass, or ascites. Of these sex cord-stromal tumors, juvenile granulosa cell tumors predominate in the neonatal period, Sertoli cell tumors present in infancy, and Leydig cell tumors present in childhood and adolescence.<sup>14</sup> Calcified Sertoli cell tumors (often seen in infants) may be associated with Peutz–Jeghers syndrome or Carney complex.<sup>15</sup> Ovarian sex cord-stromal tumors are most commonly juvenile granulosa cell tumors. Ovarian tumors of the Sertoli–Leydig cell type have been reported in patients with a cancer predisposition syndrome attributable to germline DICER1 mutations, which can also present with pleuropulmonary blastoma in childhood.<sup>16</sup> Small cell carcinoma of the ovary, hypercalcemic type, is rare but may be  $\beta\text{hCG}$ -secreting and associated with somatic and germline mutations in the SMARCA4 gene.<sup>17</sup>

**Functional germ cell tumors (gonadal or extra-gonadal):** Malignant germ cell tumors can be gonadal or extra-gonadal. They can arise in the abdomen, mediastinum, or brain (often pineal gland). Malignant germ cell tumors that secrete intact human chorionic gonadotropin (hCG), such as choriocarcinoma, can present with precocious puberty in boys, as CG activates CG/LH receptors in the Leydig cells, leading to increased testosterone production. Other functional germ cell tumors include embryonal carcinoma (CG secreting), yolk sac tumors (AFP secreting), testicular seminoma, and ovarian dysgerminoma [Table].

### Clinical presentations

Pediatric adrenocortical tumors, particularly in young children, are typically functional. The average time to diagnosis is 5 to 8 months from symptom onset. Symptoms include virilization due to excess adrenal androgens (pubic hair, acne, clitoromegaly/penile enlargement, voice changes, facial hair, and hypertension).<sup>1,18</sup> Gynecomastia and feminization can occur due to hyperestrogenism.<sup>3,19</sup> Cushingoid features can also be common due to excess glucocorticoid production, but isolated Cushing syndrome is rare (5% of patients, more commonly older children).<sup>1</sup> Many tumors secrete multiple hormones, and symptoms can overlap. Most of the sex cord-stromal tumors in boys present as painless testicular masses, but up to 20% can present with precocious puberty due to increased testosterone and DHEAS.<sup>20</sup> hCG-secreting germ cell tumors may present with modest bilateral testicular enlargement and precocious puberty in boys. Ovarian tumors can present with abdominal pain, abdominal mass, or ascites, but some may present with breast development, and/or vaginal bleeding due to excess estrogen. Children with precocious puberty (secondary sexual characteristics in girls < 8 y and boys < 9 y) should be referred urgently to a pediatrician or pediatric endocrinologist, particularly if the child is unwell or there are concerns about failure to thrive. Complete history and full physical examination (including abdominal, testicular, and neurologic assessments) are important. Tanner staging (with measurement of testicular volume or length in boys) and accurate evaluation of blood pressure for age may provide key clues on examination when less obvious signs exist.<sup>21</sup>

### Diagnostic workup and staging

Precocious puberty has a broad differential diagnosis, including primary and secondary causes. Baseline labs may include a complete blood count, electrolyte panel, liver and renal function tests. Serum levels of hormones and their metabolites may be informative. These include serum cortisol (drawn early morning to account for diurnal physiologic variation), estradiol, androstenedione, testosterone, 17-OH progesterone, aldosterone/renin ratio, and DHEAS. Serum  $\beta$ hCG and AFP levels should be sent

Table. Expected laboratory findings in pediatric functional tumors.

Tumor	Histology	Elevated (high)	Suppressed (low)
Adrenal	Adenoma	Cortisol, testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS)	Adrenocorticotrophic hormone (ACTH) (adrenal insufficiency); luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
	Adrenocortical carcinoma		
Sex cord-stromal (gonadal)	Granulosa cell	Estradiol	LH, FSH
	Sertoli	Testosterone, DHEAS, 17-OH progesterone	
	Leydig		
Germ cell (gonadal or extra-gonadal)	Choriocarcinoma	Beta-human chorionic gonadotropin ( $\beta$ hCG) testosterone (secondary to $\beta$ hCG)	LH (if $\beta$ hCG secreting)
	Embryonal carcinoma	$\beta$ HCG, testosterone (secondary to $\beta$ hCG) Alpha-fetoprotein (AFP)	
	Yolk sac tumor	AFP	
	Testicular seminomas (males)/ovarian dysgerminomas (females)	$\beta$ hCG (< 25%)	
All	All	Bone age (> 2 SD above mean for age)	Cortisol-only hypersecretion can lead to delayed bone age

to screen for malignant germ cell tumors. Bone age, based on radiographs of the hand, provides invaluable objective information. Expedited abdominal ultrasound imaging to screen for adrenal masses should be considered early.

Second-line testing could include 24-hour urine-free cortisol, 24-hour urine catecholamines (norepinephrine, epinephrine, dopamine) and metanephrines (metanephrine, normetanephrine), and spot urine vanillylmandelic acid and homovanillic acid to screen for pheochromocytoma and neuroblastoma in children with adrenal masses. An ACTH stimulation test can be useful in identifying tumors as sources of excess steroids, as they will function independently of ACTH stimulation.<sup>22</sup> Similarly, dexamethasone suppression testing can be useful in identifying tumors as sources of excess cortisol.

If a tumor is identified, staging will include cross-sectional imaging with CT, PET/CT, or MRI of the chest, abdomen, and pelvis, with visualization of lymph nodes. Head imaging may be indicated if there are neurologic symptoms or if a CNS germ cell tumor is suspected. Feasibility and optimal approach to tissue diagnosis,

whether biopsy or upfront resection, should involve the surgeon performing definitive surgery for local control. Stress dose steroids (50 to 100 mg/m<sup>2</sup>/day divided every 6 hours) may be required perioperatively in patients with adrenal suppression.

### Outcomes

Five-year overall survival for pediatric adrenocortical carcinoma is 38% to 46%, > 80% in patients with fully resected disease, and < 20% in patients with metastatic disease, which emphasizes the need for early detection.<sup>23</sup> Children with functional sex cord-stromal tumors have excellent survival outcomes with surgery alone, though they may have long-term side effects of exposure to sex hormones.<sup>24,25</sup> Adjuvant chemotherapy and radiation therapy are generally not required. Long-term disease-free survival in patients with stage II–IV disease remains 93% to 99%, with the exception of patients age > 11 years with stage IV testicular tumors, which is 83%.<sup>26</sup> Patients who are inappropriately biopsied (i.e., breach of testicular tumor capsule) or incompletely staged (i.e., without peritoneal washings at the time of

resection of an ovarian mass) are upstaged.<sup>25,26</sup> These patients, with isolated tumors that may have been treated with surgery alone, require adjuvant chemotherapy, which exposes them to additional toxicities and late effects. There is a critical window of opportunity to identify, diagnose, and intervene early in order to mitigate risk of long-term hormone exposure for patients with functional tumors and to improve survival outcomes for those with malignant tumors. Physicians should recognize precocious puberty, assess for evidence of masses on physical examination or imaging, and refer to tertiary care for ongoing care. Key points are summarized in the **Box**. ■

### Competing interests

None declared.

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### BOX. Key points: Recognition, referral, and recommended genetic screening.

#### Recognition

- Adrenocortical tumors exist on a spectrum from benign adenoma to metastatic carcinoma. Survival rates drop precipitously with metastases. Early detection is critical.
- Functional adrenal tumors are more common in children, and present with symptoms of hormone excess, including precocious puberty and Cushingoid features. Tanner staging and blood pressure could be key examination features.
- Males with testicular tumors may present with a mass, precocious puberty, or both. History alone may not reliably rule out testicular mass in adolescents and teenagers.

#### Referral

- Children with precocious puberty should be referred urgently to a pediatrician or pediatric endocrinologist.
- Children with adrenal or testicular masses should be transferred promptly to a tertiary pediatric centre. Avoid conducting fine needle aspiration and biopsies.

#### Recommendations for genetic screening

- Functional solid tumors may be associated with inherited cancer predisposition syndromes. Elicit any family history of malignancy. Children may be the index case in a family.
- Referral to medical genetics for counseling and/or further testing should be considered for patients and at-risk family members.
- Access cancer screening programs for Li-Fraumeni syndrome, which may improve survival outcomes.