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# Adrenal carcinoma as the first manifestation of a Li-Fraumeni syndrome in three paediatric patients

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Adrenocortical carcinomas (ACC) are rare aggressive neoplasms that present with rapid-onset virilization signs in 40–60% of hormone secreting paediatric cases, due to androgen-secreting masses (that frequently co-secrete cortisol) [1, 2]. Some of these ACC occurring in children result from germline mutations in the *TP53* gene, characteristic of Li-Fraumeni syndrome (LFS) (MIM#151623) [3]. The authors present a series of 3 paediatric cases of adrenocortical carcinoma as the first manifestation of LFS.

Patient number 1, a 10-month-old female infant, with Brazilian parents and no relevant priors, presented to the Emergency Department due to an acute bronchiolitis. Additionally, on examination, there were signs of virilization in the form of hirsutism, pubarche, clitoromegaly, and labia minora hypertrophy. She also presented rapidly progressive growth, going from the 15$^{th}$ percentile to > 97$^{th}$ percentile of length and from 3–15$^{th}$ to 50–85$^{th}$ percentile of weight, within a few months. Abdominal distension and tenderness on palpation prompted abdominal imaging that revealed a 7.4 × 6 cm solid mass located at the upper pole of the left kidney.

Blood analysis showed dehydroepiandrosterone sulphate (DHEA-S) > 1000 μg/dL (5–35), 17-hydroxyprogesterone (17OHP) of 720 ng/dL (5–115), androstenedione-4 > 1000 ng/dL (10–50), and testosterone of 806 ng/dL (< 20). Serum adrenocorticotropic hormone (ACTH) and cortisol were normal, and the same was seen with 24-hour urinary free cortisol, metanephrines, and catecholamines.

Magnetic resonance (MRI) confirmed a 7.7 × 5.7 × 6.9 cm mass (estimated volume: 157 mL) in the left adrenal gland, with well-defined capsule, abutting but not clearly invading the kidney. The mass was mostly homogeneous, with some areas of apparent calcification. This raised the hypothesis of a functional androgen-secreting adrenal tumour, possibly an adrenal carcinoma. Additional imaging studies (cervical and thoracic computed tomography, brain MRI, MIBG scintigraphy, positron emission tomography with fluorodeoxyglucose-PET-FDG) excluded metastatic lesions.

The patient underwent exploratory laparotomy and left adrenalectomy. Intraoperative findings revealed a tumour in intimate relation to the kidney hilum and breach of the capsule. There were no other signs of local spread. Tumour resection was complete. Pathology reported an adrenal carcinoma stage III (TNM staging system). Adjunctive therapy with mitotane was initiated, and it is still maintained nowadays (the infant is 14 months old at the time of writing). The patient underwent genetic testing that revealed the pathogenic variant R337H in the exon 10 of *TP53* gene.

Patient number 2, a previously healthy 9-month-old male infant, presented with hirsutism, pubarche, facial acne, decreased height velocity, and abdominal obesity, which prompted referral to a tertiary health centre.

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Abdominal ultrasound imaging revealed a well-defined hypoechogenic mass in the left adrenal measuring 5.5 cm (larger diameter); abdominal CT confirmed a 5 × 4 cm lesion with the same characteristics. Blood tests revealed plasma cortisol — 49.5 mcg/dL (6.2–19.4), ACTH < 5 pg/mL (< 63.3), total testosterone — 225.0 ng/dL (< 20), 17-OH-progesterone — 12.82 ng/mL (5–115), androstenedione — 8.78 ng/mL (10–50), DHEAS — 198 mcg/dL (5–35), and normal urinary catecholamines. Additional imaging studies excluded metastasis. Genetic study revealed a mutation of the *TP53* gene in the exon 10 (R337H; inherited from his mother) compatible with the diagnosis of LFS.

The infant was then submitted to left adrenalectomy in 2003. Anatomopathological evaluation revealed an adrenocortical carcinoma with 25 mitoses per 50 high-power fields invading the capsule and surrounding soft tissues. It presented vascular permeation and was not totally excised (microscopic surgical margin intersection). At that time, the literature was not clear regarding the benefits of adjuvant therapy in these specific cases. For this reason, the multidisciplinary team decided on clinical surveillance, opting for mitotane therapy in the case of relapse. Currently, the patient is 19 years old, presenting no evidence of disease recurrence.

Patient number 3, a 2-year-old female child with no previous family or medical history, was evaluated in the context of pubarche, clitoromegaly, acne, obesity, and hypertension. On physical examination, an abdominal mass was detected on palpation. After undergoing imaging (ultrasound, CT, and MRI) and blood analysis, she was diagnosed with adrenocortical carcinoma of the left adrenal gland that was resected in 2000. The mass was encapsulated, with the larger diameter measuring 6 cm. No metastasis was found. After surgery, there was a normalization of androgen levels and improvement of clinical findings. In 2009, when she came from Brazil, the patient underwent genetic testing, which revealed the same germinative missense mutation in exon 10 of the *TP53* gene. Four years later, she was diagnosed with a mature teratoma of the left ovary, which was excised surgically. Currently, the patient is 23 years old and has no evidence of recurrence of the adrenal disease and no other tumoral foci.

The diagnostic workup in children suspected of having ACC comprises evaluation of physical signs of hormonal excess, biochemical analysis (including adrenal androgens and Cushing syndrome screening), and imaging evaluation (MRI of the abdomen, pelvis, and thorax, followed by PET-FDG for diagnosis and staging). The therapeutic approach encompasses adrenalectomy, followed by mitotane in selected patients with more aggressive histology and/or incomplete tumour removal [1]. The favourable prognostic factors include smaller tumour size, complete tumour resection, age younger than 4 years, and isolated signs of virilization at presentation, among others [4]. Despite having a less aggressive clinical course, a recent study from Mayo Clinic regarding paediatric ACC reported an overall 2-year survival rate of 61% and overall 5-year survival rate of 46% [5].

Adrenocortical carcinoma (ACC) is one of the distinctive tumours of LFS, a rare disorder resulting from germline mutations in tumour suppressor gene *TP53* (with autosomal dominant inheritance pattern). This syndrome is also associated with increased risk of breast cancer, osteosarcomas, soft-tissue sarcomas, central nervous system tumours, and leukaemia. Due to the rarity of ACC and its association with LFS, all patients with ACC have an absolute indication to be tested for *TP53* gene mutations. When these are detected, genetic testing should be offered to first-degree relatives. Our 3 patients presented the same *TP53* variant (R337H), which is a common finding in children with Brazilian ancestry [3].

### *Ethics statement*
The parents of all the subjects have given informed consent to include their children's clinical cases in this paper.

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The authors have no conflicts of interest to disclose


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### *Conflict of interests*
None declared.



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