Original Article

Adrenocortical tumors in children: Imaging adenomas and carcinomas

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Abstract
Objective: This article aims to show the imaging characteristics of pediatric adrenocortical tumors.

Material and methods: We review the imaging and histological findings in patients diagnosed with pediatric adrenocortical tumors at our tertiary hospital between 2000 and 2010. We analyze the findings at ultrasonography, computed tomography, and magnetic resonance imaging that can help orient the diagnosis toward benign or malignant lesions and guide imaging follow-up.

Outcome: We found 8 adrenocortical tumors in children: 5 carcinomas, 2 adenomas, and 1 borderline tumor. Two tumors were classified as stage I, 1 as stage II, 3 as stage III, and 2 as stage IV.

Imaging enabled the diagnosis of stage IV carcinoma in 2 cases, due to the presence of initial metastases in one patient and to size of the tumor and structural changes in the other, who later developed metastases. In the other 6 cases, the imaging studies oriented the diagnosis toward carcinoma or adenoma.

Conclusions: Adrenocortical tumors are rare in children. Adrenocortical tumors include adenomas and carcinomas, and in the absence of vascular infiltration and/or metastases it is difficult to differentiate between the two types by imaging and histology. The combination of an adrenal mass and clinical signs of adrenocortical hyperfunction in a child is virtually diagnostic of an adrenocortical tumor.

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PALABRAS CLAVE
Tumores corticosuprarrenales; Pediatría; Imagen

Tumores corticosuprarrenales pediátricos: imagen de adenomas y carcinomas

Resumen
Objetivo: El propósito de la revisión es mostrar las características de imagen que presentan los tumores corticosuprarrenales pediátricos (TCSP).

Material y métodos: Se realiza una revisión retrospectiva de los pacientes diagnosticados de TCSP en nuestro hospital terciario en el periodo comprendido entre los años 2000 y 2010, desde el punto de vista radiológico y anatomopatológico.

Se estudian las características radiológicas mediante ecografía, tomografía computarizada (TC) y resonancia magnética (RM), que ayudarán a orientar la lesión hacia benignidad o malignidad, y el seguimiento de imagen.

Resultados: Se presentan 8 TCSP: 5 carcinomas, 2 adenomas y un tumor borderline; se clasifican 2 en estadio I, uno en estadio II, 3 en estadio III y 2 en estadio IV.

La radiología permitió el diagnóstico de carcinoma en estadio IV en 2 casos, dada la presencia de metástasis iniciales en un paciente y el gran tamaño y desestructuración tumoral en otro, desarrollando posteriormente metástasis. En los otros 6 casos el diagnóstico radiológico fue de aproximación respecto a su naturaleza de carcinoma o adenoma.

Conclusiones: Los TCSP son raros en la infancia. Engloban las entidades de adenoma y carcinoma, siendo difíciles de diferenciar histológicamente y radiológicamente en ausencia de infiltración vascular y/o metástasis. En un paciente con edad pediátrica la combinación de una masa suprarrenal y signos clínicos de hiperfunción corticosuprarrenal es virtualmente diagnóstica de TCSP. © 2010 SERAM. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction
Childhood adrenocortical tumors (ACTs) account for only 0.2% of all pediatric malignancies.\(^1\) Incidence rates are strikingly high in a Brazilian region, suggesting a genetic-environmental component.\(^1\)\(^-\)\(^3\)

The usual clinical manifestations are endocrine abnormalities such as signals and signs of virilization in children younger than 5 years that may be accompanied by hypersecretion of other adrenal hormones.\(^1\)\(^-\)\(^2\)

Adenoma and carcinoma may be difficult to distinguish histopathologically and radiologically.\(^2\) The presence of metastases and/or vascular invasion is highly suggestive of malignancy.

Complete resection is required for cure of childhood ACTs. The role of chemotherapy and radiation therapy continues to be investigated,\(^2\) but complete resolution of tumors after treatment with certain drugs like mitotane has been reported.\(^1\)

The combination of an adrenal mass and signs of adrenocortical hyperfunction in children is highly suggestive of ACT.

The aim of this review is to examine the imaging features of childhood ACTs.

Material and methods
We conducted a retrospective study including all the cases of childhood ACTs of our tertiary level pediatric hospital, between 2000 and 2010.

All the pediatric ACTs histopathologically classified as adenomas and carcinomas were registered. Other histologic types of adrenal masses (neuroblastoma, oncocytoma, pheochromocytoma and metastases) were excluded.

Histopathology samples of patients initially classified as having an ACT were re-examined according to the current criteria used to distinguish between adenoma and carcinoma.\(^4\)\(^-\)\(^5\)

The ultrasound, CT and MRI findings of the 8 patients diagnosed with childhood ACT were reviewed in order to collect information on the differentiation between adenoma and carcinoma. The studies were performed using a Toshiba Aquilion XU ultrasound system, a General Electric BrightSpeed 16 CT scanner (between 2000 and 2005, a Philips sequential scanner), and a Philips Achieva 1.5 T MRI system. The following parameters were evaluated with the 3 imaging modalities: tumor size (maximum longitudinal diameter), margins (ill- or well-defined, smooth or lobulated), characteristics of the interior of the mass (solid homogeneous or heterogeneous, necrosis, hemorrhage, cystic areas, calcification), vascularization on ultrasound and enhancement on CT/MRI studies, invasion of adjacent organs (kidney, liver, pancreas, spleen, diaphragm), and vascular invasion or thrombosis. At diagnosis, all the patients underwent color Doppler ultrasound; abdominal intravenous (IV) contrast CT studies were available from 4 patients, and MRI studies with and without IV contrast were available from 4 patients following the established protocol. The 8 patients underwent ultrasound and MRI follow-up examinations. No systematic CT follow-up was performed.

Results (Table 1)
Mean age at diagnosis was 4.9 years (27 days–12 year). The ratio between females (5) and males (3) was 1.66/1 (Table 1).

Tumor diameter, estimated as the average of the largest diameters obtained at ultrasound, CT and MRI, was between 3 and 18.5 cm. In 2 patients who underwent preoperative chemotherapy, the diameter of the resected specimens was smaller because of the reduction in size
provided by chemotherapy (cases 6 and 8). Specimens that arrived in the pathology laboratory in one piece weighed 90–1400 g.

All tumors had well-defined margins. The three imaging techniques demonstrated a lobulated margin in 2 carcinomas (cases 6 and 8).

Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Clinical manifestations</th>
<th>Imaging findings at diagnosis</th>
<th>Histopathology</th>
<th>Treatment</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 months</td>
<td>F</td>
<td>Virilization</td>
<td>Well-defined heterogeneous Right mass (4.8 cm). Minimal contrast enhancement</td>
<td>AC carcinoma (S III) Fragmented specimen</td>
<td>Qx</td>
</tr>
<tr>
<td>2</td>
<td>4 years</td>
<td>M</td>
<td>No. 4 months</td>
<td>Virilization</td>
<td>Well-defined, heterogeneous right mass (5 cm). Heterogeneous enhancement</td>
<td>AC Carcinoma (S III) 5 cm, 90 g</td>
</tr>
<tr>
<td>3</td>
<td>15 months</td>
<td>F</td>
<td>Virilization</td>
<td>Well-defined, homogeneous Right mass (7.5 cm). Homogeneous faint enhancement</td>
<td>Atypical ACT (indeterminate malignant potential) (S II) 8 cm, 210 g Adenoma (S I) 3 cm</td>
<td>Qx</td>
</tr>
<tr>
<td>4</td>
<td>11 years</td>
<td>M</td>
<td>Nocturnal enuresis</td>
<td>Well-defined, homogeneous right mass (3 cm). Central calcifications. Capsular enhancement</td>
<td>Adenoma (S I) 4 cm</td>
<td>Qx</td>
</tr>
<tr>
<td>5</td>
<td>27 days</td>
<td>F</td>
<td>Hh</td>
<td>Well-defined, homogeneous left mass (4 cm). Faint enhancement</td>
<td>Adenoma (S I) 3 cm</td>
<td>Qx</td>
</tr>
<tr>
<td>6</td>
<td>9 years</td>
<td>F</td>
<td>Palpable mass and AHT</td>
<td>Right mass (18.5 cm) with lobulated margins, abundant calcium and heterogeneous contrast enhancement</td>
<td>CA carcinoma (S IV) 17 cm, 1400 g</td>
<td>Pre QT + Qx + post QT</td>
</tr>
<tr>
<td>7</td>
<td>12 years</td>
<td>F</td>
<td>Prolonged metrorrhagia</td>
<td>Well-defined, homogeneous Right mass (8 cm). Central calcifications. Minimal enhancement. Partial thrombosis of IVC</td>
<td>CA Carcinoma (S III) 9 cm, 160 g</td>
<td>Pre QT + Qx + post QT</td>
</tr>
<tr>
<td>8</td>
<td>11 years</td>
<td>M</td>
<td>Asthenia and anorexia</td>
<td>Heterogeneous right mass (14.5 cm) with lobulated margin, with invasion and thrombosis of the VCI from the atrium to iliac veins, involving right internal iliac vein and right hepatic veins. Millimeter pulmonary nodes secondary to hematogenous metastases</td>
<td>CA carcinoma (S IV) 10 cm, 220 g</td>
<td>Pre QT + Qx + post QT</td>
</tr>
</tbody>
</table>

AC, adrenocortical; S, tumor stage; Hh, hemihypertrophy; AHT, arterial hypertension; SOL, space-occupying lesion; F, female; QT, chemotherapy; Qx, surgery; M, male; IVC, inferior vena cava.

No invasion of adjacent organs was observed at ultrasound and CT or MRI, except for invasion of the inferior vena cava (IVC) in 2 cases at diagnosis (cases 7 and 8) and in one case during follow-up (case 1). The tumor nature of the thrombi was confirmed by color Doppler ultrasound by demonstrating their vascularization.
Four lesions were heterogeneous with foci of necrosis and hemorrhage, and 4 were predominantly homogeneous. Ultrasound and CT demonstrated tumor calcifications in 3 cases that were extensive in one patient (case 6). Five lesions, corresponding to stage II and IV carcinomas, showed minimal and heterogeneous contrast enhancement; one lesion showed capsule-like enhancement (case 4), and 2 showed faint and homogeneous enhancement (cases 3 and 5).

Histology confirmed 2 adenomas (Fig. 1), 5 carcinomas (Figs. 2 and 3) and one tumor classified as "atypical tumor of indeterminate malignant potential" or borderline.

Of the 8 patients with ACT, 2 were classified as stage I, one as stage II, 3 as stage III, and 2 as stage IV. Stage III and IV tumors corresponded to carcinomas, and stage I to adenomas.

One patient had lung metastases and thrombosis of the IVC at diagnosis (Figs. 3 and 4). Other patient had partial thrombosis of the IVC (Fig. 3).

All the patients underwent surgical resection. Preoperative chemotherapy was required in 3 cases, and postoperative chemotherapy was required in 5 cases due to the presence of residual tumor, recurrence, metastasis, or tumor thrombosis.

During the course of the disease, one patient developed liver metastasis and other patient developed partial thrombosis of the IVC.

The 2 stage IV patients have died. Stage I, II and III patients are disease free and have been followed up over a maximum 7-year period.

Discussion

Pediatric ACTs are characterized by a variable clinical and radiologic behavior.\textsuperscript{1-3} This is reflected in our series, where we found from an ACT histologically resembling an adenoma in a newborn with hemihypertrophy (case 5), to a virilizing tumor in a patient younger than 5 years with local recurrence and disease free at follow-up (case 2), to a non-secretory ACT of large dimensions with invasion of the IVC and lung metastases that progressed to death, found in a preadolescent child (case 8).

In order to establish common criteria for the assessment of these tumors, the International Pediatric ACT Registry was created in 1990.\textsuperscript{1,3,6,7}

Based on histologic features, two subtypes of ACTs can be distinguished: adenoma and carcinoma\textsuperscript{2} (Fig. 5).
Adenomas account for 10–15% of all ACTs. They are predominantly functional, macroscopically well-demarcated, do not invade adjacent organs, are relatively small in size (<10 cm), and they weigh between 11 and 210 g. Microscopically, adenomas show no necrosis, and occasionally hemorrhage, calcification or fibrous bands. Conversely, carcinomas show macroscopic signs of malignancy such as large size, lobulated margins, and central areas of hemorrhage and necrosis. Microscopically, they exhibit nuclear atypia, pleomorphism, multinucleated forms, atypical mitoses, and vascular or capsular invasion. Although adenoma and carcinoma are distinct entities, they may be difficult to distinguish histopathologically, and the surgical specimen and tumor progression will provide the definitive diagnosis. Consequently, in children, the term adenocortical tumors is applied, including both malignant and benign tumors.

Imaging studies help to confirm the diagnosis, help in the surgical planning and in the staging of the disease. They also provide information on the features of resectability such as tumor size, invasion of adjacent structures and vascular invasion-thrombosis (cases 1, 7 and 8). A study of the chest is usually performed at the initial evaluation, since this is the most common site for metastasis, followed by the liver.

The following radiologic features may help to differentiate one subtype of ACT from the other, each having a radically different therapeutic approach and prognosis:

- Tumor size: the size, measured as the largest diameter at imaging studies, is a predictive factor of the weight or volume of the surgical specimen for tumor staging, with values varying between authors. Although in our series some carcinomas were <5 cm in diameter, none of the adenomas was >5 cm. According to literature, tumor size is an inconclusive finding but it may be suggestive of malignancy.

- Margins: ACTs usually manifest as well-marginated, non-infiltrating masses at US, CT and MRI. A lobulated morphology is, in a way, suggestive of malignancy as this feature usually accompanies larger tumors. These two features (diameter >10 cm and lobulated margins) appear together in 2 carcinomas of our series (cases 6 and 8) but in none of grade I or II ACTs.

- Internal features: pediatric ACTs can be homogeneous or heterogeneous. Heterogeneity is due to necrosis, hemorrhage, cystic areas and/or calcium. Large tumors usually exhibit a central area punctuated by areas of hemorrhage and necrosis with different
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Figure 4  Tumor thrombosis of IVC (case 8). (a1–a3) Axial (a1) and coronal (a2) TSE T2-weighted sequences and sagittal ultrasound (a3) show increased diameter of the VCI secondary to thrombosis (black arrow) and the upper position of the thrombus pointing toward the right atrium (white arrows), with a cranial-caudal diameter that reaches 14 cm up to the internal iliac vein. (b1–b3) Contrast-enhanced CT angiography demonstrates thrombus persistence in the IVC after 7 cycles of chemotherapy, with cranial extension in the thoracic IVC (arrow in the coronal reconstruction) (b1) and in the right hepatic vein that shows no enhancement, in contrast with the middle hepatic vein that show contrast enhancement, in the axial plane (b2). There is reduction in tumor size after chemotherapy (including mitotane) received prior to surgery (asterisk) (b3).

- Echogenicity/attenuation/signal. This was also the predominant pattern in the large carcinomas in our series. Calcifications are common and apparently not related with the presence of benign adenomatous or malignant carcinomatous histologic features. Their appearance ranges from small focal inclusions (case 4, adenoma) to extensive amorphous deposits (case 6, carcinoma).
- Local invasion and metastasis to lymph nodes: according to literature, invasion of adjacent organs and lymph node spread are associated with poor prognosis. None of the patients in our small series developed these invasive features.
- Vascular invasion-thrombosis: ultrasound is the primary imaging technique for assessment of this feature. Additionally, Doppler color can be used to distinguish between tumor thrombi (vascularized) and non-tumor thrombi (avascular). The 3 thrombi detected in our series were tumor thrombi and presented in the setting of carcinoma. Vascular invasion-thrombosis is indicative of aggressive lesions.

Figure 5  Histopathology of adrenal adenoma (case 4) and carcinoma (case 7). (a) Macroscopic photograph of an adenoma shows a circumscribed, small (3 cm) solid mass with a yellowish tinge. (b1 and b2) Macroscopic photograph of a carcinoma shows a solid mass with areas of necrosis and hemorrhage, 9 cm in diameter and 160 g in weight. Microscopic photograph (HE, 20×) shows cytologic atypia in this area of the neoplasm.
The following non-radiologic features are also part of pediatric ACTs setting and should be included in the assessment of these tumors:

- Pediatric ACTs typically occur during the 4–5 years of age, with a second peak during adolescence. In our series, the age of pediatric patients falls within the results referenced in the literature. Some authors have suggested that children younger than 5 years have better prognosis, but this finding has not been demonstrated in this series.
- Up to 90% of children with an ACT present with signs and symptoms of virilization associated with overproduction of androgens. Non-functional tumors appear only in 10.2% of pediatric patients, being more common in older children (case 8). The type of secreted hormone seems to correlate with prognosis, with glucocorticoid-secreting tumors associated with worse prognosis than tumors secreting exclusively androgens, but no cases in this series exhibited this feature.
- Syndromic associations. Scientific literature demonstrates association between ACT and hemihypertrophy, Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome, but less association with the Carney complex, congenital adrenal hyperplasia, ganglioneuroma, ganglioneuroblastoma and MEN 1 syndrome. Only an association with hemihypertrophy was found in our series (patient 5).

The staging system of ACTs, modified several times, is based upon the assumption that complete resection and tumor size are the most important factors, and imaging studies play therefore a role both in the preoperative (size) and postoperative (residual tumor) assessment.

Surgical resection is the mainstay of therapy, providing excellent results in low-stage tumors and if complete tumor resection is achieved. The role of chemotherapy has not been systematically evaluated. Mitotane is an isomer of the insecticide DDT that induces adrenocortical necrosis. Mitotane was used in cases 6 and 8, both stage IV at diagnosis.

Regarding the prognostic factors, complete tumor resection is the most important factor for disease control. This makes follow-up imaging particularly important.

In conclusion, adenoma and carcinoma may be difficult to distinguish radiologically in the absence of metastasis or vascular invasion. Large tumor size, internal heterogeneity and lobulated margins are radiologic features suggestive of carcinoma rather than adenoma.

Given the clinical features and laboratory findings of children with ACT, when these patients arrive in the Radiology Department they have already a presumptive diagnosis of adrenal tumor. In a pediatric patient, the combination of an adrenocortical mass and signs and symptoms of adrenocortical hyperfunction is diagnostic of ACT.

Authorship

1. Responsible for the integrity of the study: MIML.
2. Conception of the study: MIML.
3. Diseño del estudio: MIML.
4. Acquisition of data: MIML, SRC.
5. Analysis and interpretation of data: MIML, SRC, WL, LCR.
6. Statistical analysis: N/A.
7. Bibliographic search: MIML, WL.
8. Drafting of the paper: MIML.
9. Critical review with intellectually relevant contributions: MIML, SRC, WL, LCR, MDDP, OES.
10. Approval of the final version: MIML, SRC, WL, FIC, LCR, MDDP, OES.

Conflicts of interest
The authors declare no conflicts of interest.

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