

Case Report

Pheochromocytoma in Childhood

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Pheochromocytoma is a neoplasia of chromaffin cells that is very rare in children. Its signs and symptoms result from the release of catecholamines. We report the case of a child with pheochromocytoma of difficult clinical management, confirmed on the anatomicopathological study, and cured after surgical resection.

Pheochromocytoma is a neoplasia of chromaffin cells with signs and symptoms resulting from the release of catecholamines. It is usually a solitary, unilateral, encapsulated tumor, which, in 90% of the cases, is located in the adrenal medulla. It is a rare cause of hypertension (0.1%). Pheochromocytoma is rarely reported in children, because only 10% of those tumors occur in the first decade of life, and it usually affects individuals of the male sex^{1,2}. It may be inherited with autosomal dominant transmission, and, in such cases, multiple tumors are common. It may be associated with other diseases, such as in von Hippel-Lindau syndrome (autosomal dominant disorder characterized by angiomas of the retina, hemangioblastomas of the central nervous system, renal cysts, renal carcinomas, pancreatic cysts, and pheochromocytoma in 10 to 20% of the patients), multiple endocrine neoplasias, tuberous sclerosis, and Sturge-Weber syndrome. The latter syndrome or encephalo-facial hemangiomas may result from a disorder in migration and differentiation of the tissues originating from the neural crest; it consists of the following findings: ectasia of the leptomeninge and choroid; ocular involvement (glaucoma, hemangiomas in the episclera and choroids); plane hemangioma in the trigeminal distribution; neurological impairment that may manifest as epilepsy, mental retardation, hemiplegia, and hydrocephaly³. The predominant clinical findings result from the excessive production of epinephrine and norepinephrine, which lead to crises of hypertension, cephalgia, palpitations, abdominal pain, paleness, vomiting, sweating, and weight loss². Its diagnosis requires a certain degree of suspicion and depends on the evidence of production of catecholamines by the tumor, and the differential diagnosis should include other neoplasias, hyperthyroidism, and diabetes mellitus and insipidus². Cure depends on tumor resection⁴.

Case Report

The patient is a 6-year and 8-month-old male child, who sought the outpatient care clinic due to anorexia, weight loss

(4kg), and profuse nocturnal sweating for 6 months. The patient also reported episodes of fatigue, vomiting, exanthema, and fever. On admission, a physical examination revealed the following: weight loss, cervical and axillary polyadenomegaly, hepatomegaly, and a palpable mass in the left hypochondrium compatible with splenomegaly. The first diagnostic hypothesis was lymphoma. The patient's food intake and development were adequate.

On physical examination, his weight was 18,800 g (percentile 5), his heart rate was 120 bpm, his respiratory rate was 48 ipm, and his blood pressure was 110/60 mm Hg. He had mild intercostal draught, and his pulmonary auscultation showed no important changes. His cardiac auscultation was as follows: presence of the third cardiac sound, systolic murmur (++) in the mitral region, which irradiated to the axillary region. His liver could be palpated 8 cm from the right costal margin, and his spleen 6 cm from the left costal margin. The chest radiograph showed enlargement of the cardiac area, and the electrocardiogram and echocardiogram were compatible with dilated cardiomyopathy. During the night, the patient had febrile peaks, agitation, sweating, and assumed the genupectoral position. A chest X-ray showed a decrease in transparency to the right and enlargement of the cardiac area. The electrocardiogram showed sinus tachycardia, and the echocardiogram showed the following measurements: SLV, 33mm; DLV, 41 mm; EF 39%; RA, 19 mm; and estimated pulmonary pressure, 40 mm Hg. The patient received furosemide, digoxin, captopril, and crystalline penicillin.

The patient evolved with erythematous-pruriginous lesions in the dorsum, hypertensive peaks (range: from 140/100 mm Hg to 170/120 mm Hg), accompanied by intense discomfort, paleness, sweating, vomiting, cephalgia, and high fever. The patient had an infectious complication and respiratory functions worsened, requiring the use of a ventilatory prosthesis for 3 days, and sedation with midazolam and fentanyl. The patient lost weight, reaching 16,400g. His hemogram was as follows: red blood cells, 3,920,000 per mm³; HCT, 31%; HB, 10.4 g%; platelets, 348,000 per mm³; reticulocytes, 3.2%; leukocytes, 11,800 per mm³, with a normal differential. His serum levels of glucose, urea, creatinine, proteins, transaminases, gamma GT, bilirubin, TSH, and T3 and T4 were normal, as was his electrolytic profile. The serologies for HIV, HBs Ag, Anti HBs, and Anti HAV were negative. His cranial and chest CT scans were normal, and the abdominal CT scan showed a mass in the topography of the left adrenal gland, which, with contrast medium, showed irregular areas of uptake, compatible with necrosis. The image suggested pheochromocytoma, and the child received prazosin, 5 µg/kg/dose.

During the evolution, he had crises of tachycardia, which

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were controlled with atenolol. He began to gain weight, reaching 21,100 g on the 25th day of follow-up. His funduscopy was normal. The serum levels of cortisol, normetanephrine, metanephrine, and vanillylmandelic acid were increased, while those of epinephrine, norepinephrine, and dopamine were normal. Scintigraphy with metaiodobenzylguanidine showed a single mass in the topography of the left adrenal gland (fig. 1).

The patient was referred for surgery for mass resection 6 weeks after admission. Prazosin was suspended one day before surgery, and continuous infusion of sodium nitroprusside was initiated for blood pressure control in the perioperative period. During surgical manipulation, the patient had several hypertensive crises (200/140 mm Hg). The mass was removed, and BP simultaneously dropped to values around 40/120 mm Hg. Sodium nitroprusside was suspended and noradrenaline infusion was initiated.

The surgical specimen weighed 30 g, measured 5.5 x 2.5 x 0.7 cm, and was sent for histopathological examination. Microscopically, the mass showed neoplastic cells of light finely granular cytoplasm and pleomorphic hyperchromatic nuclei (fig. 2). The immunohistochemistry stainings (neuron-specific, chromogranin, and enolase) were positive, confirming the neuroendocrine origin of the tumor (fig. 3). The postoperative follow-up was carried out on an outpatient basis, with programmed medical visits every 2 months. The drugs prescribed (captopril, digoxin, and furosemide) were gradually suspended within 6 weeks, and currently the patient has adequate blood pressure levels and weight for his age.

Discussion

Of all endocrine diseases, pheochromocytoma is the one causing the most dramatic and life-threatening crises, because, in addition to severe hypertension, cardiac complications may occur leading to hypotension and shock². Our patient had weight loss and other typical signs and symptoms of pheochromocytoma, consequent to excessive release of catecholamines. However, as the patient was a child, and because pheochromocytomas are rare in children, the diagnostic hypothesis on admission was neoplasia, and then hyperthyroidism. Even in cases of appetite increase, weight loss occurs, and the patient may become cachectic. Ten percent of the cases have been reported in children from 6 to 14 years of age, being more frequent in the right adrenal gland. Our 6-year-old patient had a palpable mass in his left hy-

pochondrium, which was mistaken for splenomegaly. So far, other cases in the patient's family have been ruled out. This is important information, because the disease may be inherited in approximately 10% of the cases⁵.

The patient's history had started 6 months before admission, and the symptoms worsened progressively. In the literature review, most patients had their diagnoses and treatments delayed because of lack of diagnostic suspicion⁶. Our patient had signs of heart failure and dilated cardiomyopathy with a significant decrease in systolic functions. The signs of dilated cardiomyopathy have also been attributed to myocarditis, accompanied by left ventricular failure and acute pulmonary edema⁷. The microscopic examination showed necrosis of fibers, inflammatory infiltrate, and fibrosis.

In experimental studies, when norepinephrine is infused into the rabbit, sustained coronary vasoconstriction occurs, causing histologically similar lesions in the myocardium⁸. In experimental myocarditis or cardiomyopathy induced by catecholamines, a beneficial effect of captopril has been reported, which may be due to the fibrosis caused by the excess of catecholamines. The patient

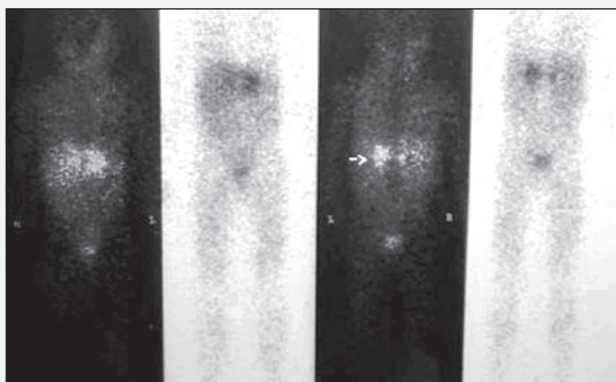


Fig 1 - Scintigraphy with metaiodobenzylguanidine showing a single mass in the topography of the left adrenal gland.

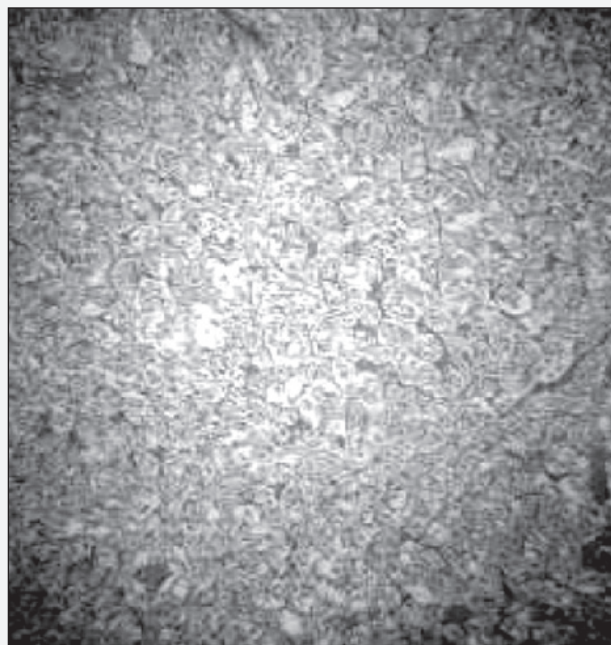


Fig 2 - Microscopic findings of the adrenal gland: chromaffin cells with pleomorphic and hyperchromatic nuclei (H&E, 40x).

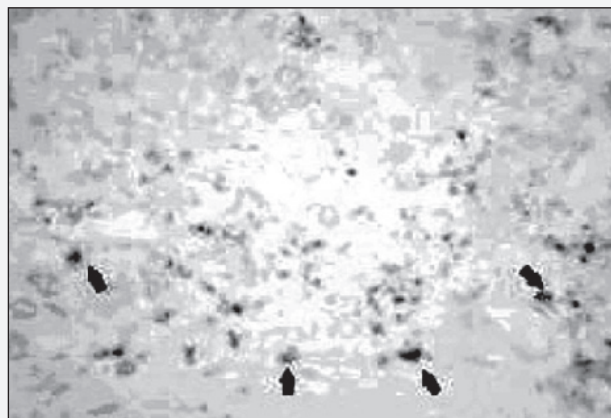


Fig 3 - Microscopic findings of the adrenal gland: positive immunoreaction (immunohistochemistry, 40x).



may have severe hypotension, consequent to intense vasoconstriction. The electrocardiogram usually shows signs of left ventricular hypertrophy, T-wave inversion, and changes in the ST segment. The echocardiogram may show signs of left ventricular hypertrophy, a decrease in ventricular functions, impairment of the anterior mitral leaflet, and paradoxical septal movement⁹. In our patient, the signs of cardiomyopathy disappeared during the 6 weeks after surgery, as has already been reported in the literature⁵.

Our patient had one single tumor, and the definitive diagnosis was established by measuring the urinary levels of catecholamines, scintigraphy, and histopathological study. The radioactive isotopes locate the chromaffin tissues, and confirm or rule out the existence of tumors in other sites¹⁰. A recently published multicenter study has shown that the biochemical measurements are the best tests for diagnosing that disease, mainly the measurement of metanephrines, which has a sensitivity of 99% for the free form in the plasma, and of 97% for the urinary fractionated form. The specificity of the measurement of the vanillylmandelic acid in the urine is 95%⁴. In several cases, the diagnostic investigation per se may be disastrous, because on mass palpation or during other manipulations, catecholamines are released, causing dramatic consequences. Caputo et al¹¹ reported the case of a patient with pyelonephritis, who, when undergoing contrast tomography, had a crisis of dyspnea, acute pulmonary edema, and deterioration in his general condition with crises of fever, alternation of hypo- and hypertension, and evolved to death. It was a case of multiple systemic neoplasia with bilateral pheochromocytoma, diagnosed on necropsy, whose worsening was due to excessive discharge of catecholamines during clinical investigation after venous administration of contrast medium.

Medications should be carefully administered, because crises have been reported after the use of opiates, adrenocorticotrophic hormones, dopaminergic agonists, tyramine, anesthetics (mainly halothane), and cocaine¹². The use of beta-blockers before alpha-blockade may worsen hypertension. The treatment recommended in the preoperative preparation is the blockade of the alpha receptors by using phenoxybenzamine or prazosin for 2 weeks before surgery. The beta-blocker may be necessary for controlling tachycardia. During surgery, a potent inhaling anesthetic agent should be used, and the hypertensive crises occurring during manipulation of the tumor should be controlled with nitroprusside or phentolamine, and tachycardia or tachyarrhythmia with esmolol or metoprolol⁵. The surgical management has been considered a challenge for several years, and it began to succeed after the knowledge and application of adequate pre- and perioperative preparation⁶. Our patient received prazosin in the preoperative period for 6 weeks, a long period of time, because we had some difficulty in performing scintigraphy, but, during that time, a significant weight gain occurred. During surgery, the patient experienced the already expected crises, which were successfully controlled with the medications cited.

The literature reports that pheochromocytoma, in 75% of the cases, originates in the right adrenal medulla, and its dimensions may vary from microscopic sizes to large tumor masses¹³. Our patient's tumor originated from the left adrenal medulla, was single and encapsulated. The histopathology confirmed that the tumor consisted of chromaffin cells with pleomorphic hyperchromatic nuclei and fine granular cytoplasm, in a trabecular arrangement forming acini. The immunohistochemical staining confirmed its neuroendocrine origin¹⁴.

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