Clinical Case Report

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Diagnostic challenges and good treatment outcomes in pediatric paraganglioma of the abdomen

A case report

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Abstract

Rationale: Paraganglioma is a catecholamine-producing neuroendocrine tumor. Management of paraganglioma including its diagnosis is difficult, because it has no characteristic symptoms and many diseases can manifest as headache and high blood pressure. Herein, we report a rare case of paraganglioma of the abdomen with headache and initial normal blood pressure.

Patient concerns: A 9-year-old Chinese girl was hospitalized because of intermittent headache persisting for more than 9 months and recurrent headache for 15 days, accompanied by weight loss, impaired heat tolerance, and otherwise normal blood pressure.

Diagnoses: We eventually diagnosed paraganglioma.

Interventions: Her paroxysmal hypertension subsided over 1 month after surgical removal of the tumor.

Lessons: Intermittent headache and normal hypertension as the initial symptoms of paraganglioma can easily lead to misdiagnosis as another disease (e.g., renal artery stenosis, primary hyperaldosteronism, Takayasu's arteritis), and its differential diagnosis is difficult. When a patient presents with intermittent hypertension, clinicians should consider a diagnosis of paraganglioma. The comprehensive use of ultrasonography, computed tomography (including enhanced computed tomography and 3D reconstruction), magnetic resonance imaging, and plasma catecholamine measurement can aid the diagnosis of paraganglioma.

Abbreviations: BP = blood pressure, CA = catecholamine, CT = computed tomography, GAPP = grading system for adrenal PCC and PGL, HR = heart rate, HTN = hypertension, MNs = metanephrines, PCC = pheochromocytoma, PGL = paraganglioma, SNP = sodium nitroprusside, WHO = World Health Organization.

Keywords: hypertension, paraganglioma, pediatric

1. Introduction

Paraganglioma (PGL), first reported by Frankel in 1886,[1] is a rare neuroendocrine tumor characterized by paroxysmal or continuous hypertension (HTN) and sympathetic activation. The main diagnostic manifestations of PGL include HTN, headache, hypermetabolism, hyperglycemia, and excessive sweating. Children with pheochromocytoma (PCC) or PGL, as well as adults, often present with an array of symptoms that may make diagnosis difficult. Thus, children are easily misdiagnosed upon presentation of nonspecific symptoms such as headache, vomiting or nausea, weight loss, vision disorder, abdominal pain, and constipation. Surgery remains the mainstay treatment for PGL. Here we report the rare case of a young Chinese girl who was diagnosed with a PGL based on immunohistochemical analysis.

2. Case presentation

A 9-year-old Chinese girl was admitted to the Central South University Xiangya School of Medicine Affiliated Haikou Hospital (Haikou, China) on December 14, 2016 with intermittent headache persisting for more than 9 months and recurrent headache for 15 days, accompanied by weight loss and impaired heat tolerance. Written informed consent for publication of the case details was obtained from the patient's family.

With no notable medical history, the girl suddenly experienced headache in the bilateral temporal region with no obvious cause more than 9 months before admission. Headache lasted 1 hour before spontaneous remission and was accompanied by eye pain. The patient had a headache attack at approximately 10-day intervals. Head computed tomography (CT) at a local hospital showed only inflammation of the right side of the maxillary sinus and ethmoid sinus. The results of 24-hours amplitude-integrated electroencephalography at our outpatient hospital were normal. Physical examination on admission showed: normal blood pressure (BP); heart rate (HR) of 98 beats/min; and III/6 level systolic murmurs heard in the heart area. The other parameters were normal. Routine blood tests revealed a red blood cell count of 4.93×10^{12}/L (reference, 4–4.5×10^{12}/L), hemoglobin level of 144 g/L (reference, 120–140 g/L), platelet count of 392×10^{9}/L

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(reference, 125–350 $\times 10^9$/L), white blood cell count of 11.36 $\times 10^9$/L (reference, 3.5–9.5 $\times 10^9$/L), lymphocyte percentage of 14.3% (reference, 20%–50%), and neutrophil percentage of 81.6% (reference, 40%–75%). On routine urine test, the sample was protein++ (reference, negative). On 24-h urine analysis, the total protein load was 410 mg (reference, 0–150 mg). The cerebrospinal fluid showed a pressure of 150 mmH_2O (reference, 70–200 mmH_2O) and normal levels of conventional and biochemical markers. Head magnetic resonance imaging showed obscure flake signals for slightly long T1 and long T2 at the bilateral cerebellar hemisphere and an otherwise high signal on water suppression imaging. The patient was initially diagnosed with viral encephalitis and congenital heart disease and treated with ceftriaxone sodium and acyclovir for anti-infection. The symptom of headache almost disappeared with this treatment, but BP remained high (maximum BP, 200/185 mm Hg) 12 days after admission. PCC was suspected because of HTN. Funduscopic examination on day 11 post-admission showed that the double optic disk was slightly fuzzy and reddish, with a flat retina, retinal edema, and no retinal hemorrhage or retinal bleeding. The patient was transferred to the pediatric intensive care unit on day 11 and treated with continuous intravenous sodium nitroprusside (SNP) and phentolamine and oral phenoxybenzamine and metoprolol to control BP and HR. Plasma catecholamine (CA) measurements showed an adrenaline level of 47.81 pg/mL (reference, 0–100 pg/mL), a norepinephrine level of 642.19 pg/mL (reference, 0–600 pg/mL), and a dopamine level of 46.54 pg/mL (reference, 0–100 pg/mL). The abdominal aorta and double renal artery were almost normal on abdominal color Doppler ultrasound. Both abdominal color Doppler ultrasound and CT (including enhanced CT and 3D reconstruction; Fig. 1) showed a mass (46 × 31 mm) next to the bladder in the right lower abdomen. Ultrasonic cardiography showed that the left side of the heart was slightly enlarged with thickening of the left ventricular wall, which was thought to reflect hypertensive heart disease. The patient's BP ranged from 98/60 to 130/87 mm Hg, and her HR ranged from 72 to 110 beats/min over 2 weeks. The patient was diagnosed with PGL, hypertensive crisis, hypertensive heart disease, and hypertensive renal disease and treated first with urological surgery on day 21 post-admission. Replenishment of body fluids and electrolytes was started 3 days before surgery, and oral phenoxybenzamine and metoprolol were stopped before surgery. Tumor resection was performed with a trachea cannula on day 34 post-admission under general anesthesia. Anesthetists controlled BP via intravenous pumping of SNP and phentolamine and monitored central venous pressure during surgery. The central venous pressure was low (3 cmH_2O) before surgery, and the anesthetist transfused 3500 mL liquid with polygeline and sodium lactate Ringer's injection (including 1 U of red blood cell suspension and 100 mL plasma). One oval mass was found where the right iliac vessels crossed. The sheath of the iliac vein was separated carefully along the external iliac artery and the tumor was separated from the iliac vessels. The tumor and its surrounding tissues were then clipped along the tumor capsule and separated gradually. The lower part of the tumor was adhered to the right ovary, so the surgeons carefully separated the capsule from the ovary and severed the blood vessel before removing the tumor. Lastly, the right ovary was fixed to the pelvic wall. The patient's BP remained steady until the tumor blood vessel was severed. The anesthetist stopped intravenous pumping of SNP and phentolamine to use norepinephrine to increase the BP (along with colloid solution and crystalloid fluid). Intravenous norepinephrine was continued for 24 hours post-surgery to maintain normal BP. On day 43, the BP ranged from 90/60 to 130/85 mm Hg. The excised tumor was 4.8 × 4.1 × 3.5 cm and had a complete capsule. On light microscopy, the tumor cells showed a regular zellballen pattern, absence of sustentacular cells, slightly enlarged nuclei, and an obvious capsule, acidophilic and relatively abundant cytoplasm. Nuclei that were round or elliptical were found in the middle, and mitotic cells were few. Tumor cellularity was 150 to 200 cells/U under high power magnification (×400; Fig. 2). On immunohistochemical analysis (Fig. 3), the tumor was partly S-100(+), SyN(+), CgA(+), CD56 (+), CD10(−), approximately 5% Ki67(+), and CK(−), and sustentacular cells were seen around chief cells, which is in accordance with PGL. The patient was discharged after 1 week once her BP was steady. The symptom of hypermetabolism disappeared. At later follow-up, the patient had gained weight well to about 25 kg, and her BP was 100/60 mm Hg. Plasma CA measurements on day 54 showed an adrenaline level of 45.35 pg/mL (reference, 0–100 pg/mL), a norepinephrine level of 141.51 pg/mL (reference, 0–600 pg/mL), and a dopamine level of 46.54 pg/mL (reference, 0–100 pg/mL).

3. Discussion

In 2004, the World Health Organization (WHO) designated neuroendocrine tumors originating in the adrenal gland as PCC and neuroendocrine tumors originating from extra-adrenal tissue (usually in the chest, abdomen, and pelvic cavity) as PGL.[2]

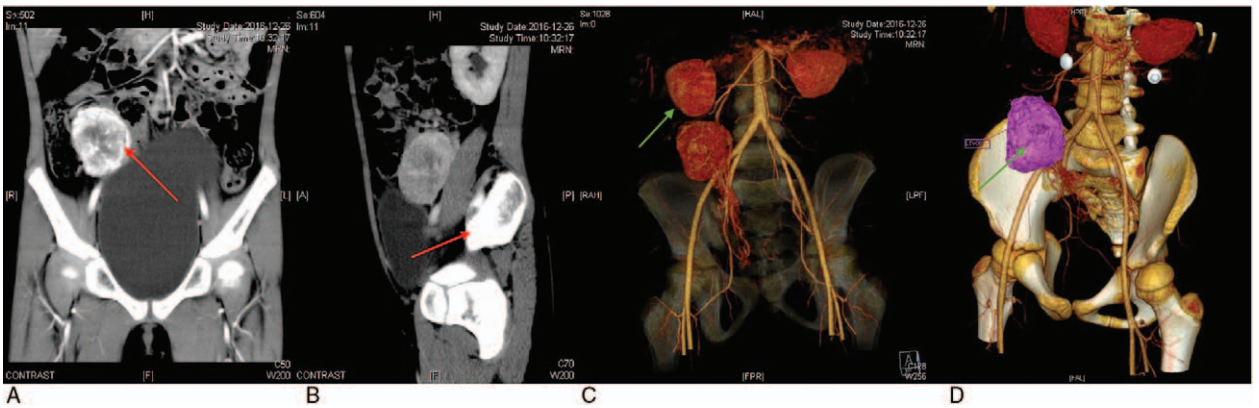

Figure 1. Enhanced CT and 3D reconstruction of the abdomen. Arrow points to tumor in the right lower abdomen. CT = computed tomography.

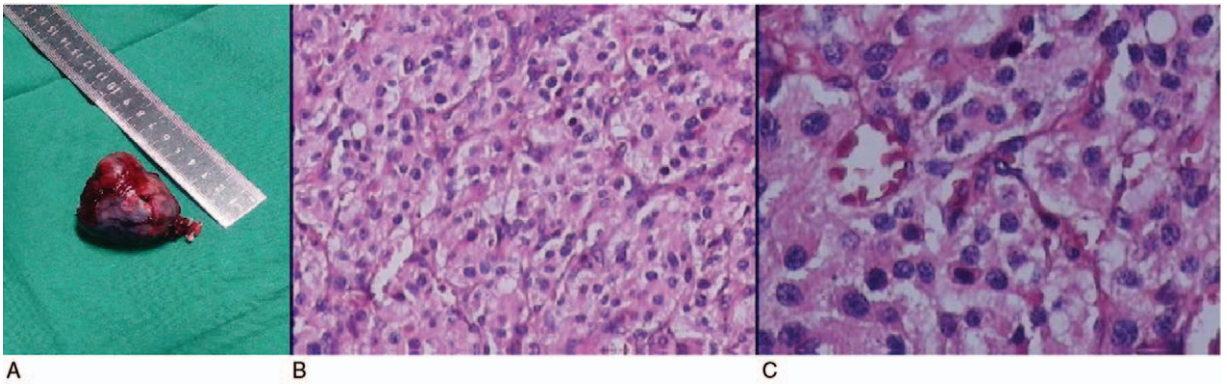

Figure 2. (A) Excised tumor. (B and C) PGL tumor cells distributed in nests that were abundant in the sinusoid interval. The histological pattern was a regular zellballen pattern (hematoxylin and eosin, 200×). (C) Tumor cells were polygonal in shape, with abundant eosinophilic granular cytoplasm and nuclei of the same size, and tumor cellularity was 150 to 200 cells/U under high power magnification (hematoxylin and eosin, 400×). PGL = paraganglioma.

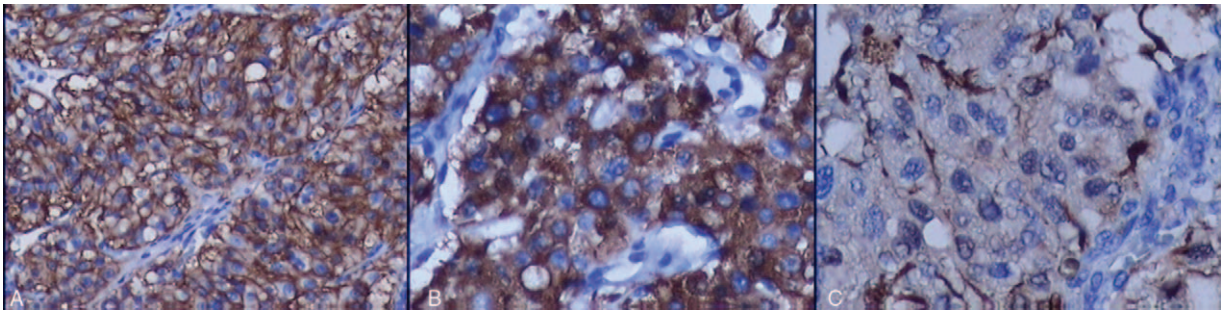

Figure 3. Tumor cells were diffusely positive for Cgn (A) and for SyN (B). The sustentacular cells were s-100 positive (C).

Distinction between these tumors is important due to differences in the risks of malignancy. Both tumors can secrete CA and cause secondary HTN, and both are very rare in children.[3] Only one case of pediatric PCC with headache as the first symptom could be found in the literature.[4] However, differential diagnosis of headache in childhood must include PCC/PGL, and headache, in fact, may be the presenting symptom. These tumors are more commonly found in older preadolescence when large amounts of growth hormone are secreted.[5]

Diagnosis of PCC and PGL in pediatric cases is best confirmed by measurement of 24-h fractionated urinary metanephrines (MNs) and CA. Measurement of plasma or urine CA and metabolites is highly sensitive and specific in patients with symptoms, with 98% of cases being positive for vanillymandelic acid and MNs in urine. Ross[6] proposed that blood testing for CA and their metabolites is more sensitive than urine testing. In addition, measurement of plasma fractionated MNs is more sensitive than measurement of urine CA in children.[2] Based on our hospital conditions, plasma CA levels rather than urine CA levels were measured in the present case.

Headache is common among children, and its etiology, classification, and diagnosis are complex. Our patient had intermittent headache with possible paroxysmal HTN for >9 months. Unfortunately, the patient's BP was not measured prior to admission and was normal at admission. Although sustained HTN is common in PGL cases, it may not be found if patients complain only of headache and have a normal BP. Due to the pulsatile release of CA, BP can be normal during the intervals between release, and this variation in BP can actually be helpful in the diagnosis. HTN was found when our patient's BP was measured conventionally during hospitalization and conformed to the clinical manifestation of paroxysmal HTN in PGL. It was crucial to control the patient's BP and HR at ideal levels before surgery. We aimed to control the BP to <120/80 mm Hg, HR to <90 beats/min, and hematocrit to <45%.

Surgical resection is the primary treatment for PGL. Use of the tracheal cannula was adopted by our surgeons rather than open surgery, because it is associated with a shorter operating time and reduced trauma and complications.[7]

No reliable gross or histologic criteria have been established for malignancy of PGL other than invasion of adjacent structures or metastases in the current WHO definition. Recently, a grading system for adrenal PCC and PGL (GAPP) with the criteria of histologic pattern, cellularity, comedo necrosis, capsular or vascular invasion, Ki67 labeling index, and CA type was used to grade tumors as well differentiated (0–2 points), moderately differentiated (3–6 points), or poorly differentiated (7–10 points), and 2 points was defined as a finding suggestive of malignancy.[8] The GAPP grade for the present case was 4 points (moderately differentiated), and the tumor was located outside the adrenal gland. Thus, malignancy cannot yet be ruled out in the present case. Thus, we advised the patient to return for regular follow-up.

At present, about 40% of patients with PCC/PGL have germline mutations in at least one of 14 susceptibility genes,[9]

and the rate of germline mutation in pediatric patients with PCC/PGL is up to 70%.[10] The common susceptibility genes include *SDHB*, *SDHD*, *VHL*, and *RET*. PGL mainly secretes norepinephrine, and the genes *SDHB*, *SDHD*, *SDHC*, *VHL*, and *MAX* are involved. The possibility of *SDH* mutation was also not ruled out in the present case because *SDH* mutations are most common in PCC/PGL, and the rate of malignancy is about 50% for *SDHB*-related sympathetic PGL. Immunohistochemistry is progressively used as a screening tool prior to germline testing, and immunohistochemical staining for *SDHB* has been validated as a sensitive, reliable marker for germline mutation of any of the *SDH* subunit genes. We once advised the patient to do the related genetic tests, but her parents refused due to the cost.

In conclusion, clinicians should be aware that the clinical manifestations of PGL can vary considerably. Many pathogens can cause secondary HTN in children, but paroxysmal HTN may suggest PGL. Immunohistochemical analysis should be conducted to confirm the diagnosis.

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Author contributions

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Investigation: Jun Lu.
Methodology: Qingyang Cui, Jun Lu.
Project administration: Qingyang Cui.
Resources: Qingyang Cui, Chong Zhang.
Software: Chong Zhang.
Supervision: Chong Zhang.

References

[1] Wang JH, Fu Q, Gu BJ. Retroperitoneal malignant paraganglioma: a case report and review of the literature. Chin J Clinicians 2012;6:7442–4.
[2] Gimenez-Roqueplo AP, Lehnert H, Mannelli M, et al. Phaeochromocytoma, new genes and screening strategies. Clin Endocrinol (Oxf) 2006;65:699–705.
[3] Ciftci AO, Tanyel FC, Senocak ME, et al. Pheochromocytoma in children. J Pediatr Surg 2001;36:447–52.
[4] Xu LS, He JT, Jing M, et al. Pheochromocytoma with headache as first symptom: a case report and literature review. J Jilin Univ (Medicine Edition) 2015;41:1027–31.
[5] Reddy VS, O'Neill JAJr, Holcomb GW3rd, et al. Twenty-five-year surgical experience with pheochromocytoma in children. Am Surg 2000;66:1085–91. discussion 1092.
[6] Ross JH. Pheochromocytoma. Special considerations in children. Urol Clin North Am 2000;27:393–402.
[7] Stanford A, Upperman JS, Nguyen N, et al. Surgical management of open versus laparoscopic adrenalectomy: outcome analysis. J Pediatr Surg 2002;37:1027–9.
[8] Kimura N, Takayanagi R, Takizawa N, et al. Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2014;21:405–14.
[9] Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer 2014;14:108–19.
[10] Cascon A, Inglada-Perez L, Comino-Mendez I, et al. Genetics of pheochromocytoma and paraganglioma in Spanish pediatric patients. Endocr Relat Cancer 2013;20:L1–6.