

A pediatric malignant paraganglioma and brief review of the literature

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Abstract

A 10 years old boy presented to our hospital complaining of belly pain. He had a retroperitoneal mass diagnosed by ultrasound 3 days before. During that time he was found to have slight hypertension. Computed tomography (CT) showed a left retroperitoneal mass with edge enhancement and central necrosis indicating pheochromocytoma (PCC). Vanillylmandelic acid (VMA) in the 24 hours urine sample was not elevated. Pheochromocytoma was suspected given his hypertension and the ultrasound and CT findings. Fluorine-18- fluorodeoxy glucose positron emission tomography (¹⁸F-FDG PET) showed intense uptake in the left adrenal area (SUVmax 32.9) with a central ¹⁸F-FDG uptake defect. Subsequently, left adrenalectomy was successfully performed. Histological examination showed that the tumor was a paraganglioma (PGL) with low-grade malignancy. **Conclusion:** Fluorine-18-FDG PET is a highly sensitive method to detect PGL, but could not make a differential diagnosis between PGL and PCC although high uptake of ¹⁸F-FDG may indicate malignancy. As our case clearly demonstrates, rare causes of including PCC or PGL should be considered in the setting of secondary hypertension.

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Introduction

Pheochromocytoma/paraganglioma (PCC/PGL) as rare neuroendocrine tumors that arise from sympathetic and parasympathetic paraganglia [1] associated with either the sympathetic or the parasympathetic nervous systems [2]. Paraganglioma comprises an extra-adrenal subset of PCC and is often characterized by secretion of catecholamines, although sometimes is biochemically inactive. This makes diagnosis challenging [3]. Paraganglioma is rare in the pediatric population occurring in approximately 1 in 50,000 children [4]. Clinical presentation includes symptoms related to catecholamine hypersecretion and/or tumor mass effect. Approximately 40% of PGL carry a germline mutation [5] associated with transcriptome changes that are currently subdivided into 2 main clusters [6]. Most pediatric PGL are benign [1]. Surgical resection, with appropriate perioperative management of catecholamine-related symptoms, remains the treatment of choice [1]. We report a rare pediatric PGL.

Case Report

A 10 years old boy presented to our hospital complaining of pain in the abdomen. He had a retroperitoneal mass diagnosed by ultrasound 3 days before. During that time he had mild hypertension. The retroperitoneal mass was confirmed in our hospital by ultrasound (Figure 1) indicating PCC. The patient was then charged in the Department of Pediatric Surgery. He denied having headache or tachycardia and was presented in good clinical condition. Physical examination revealed nothing positive. His vital signs included a heart rate of 97 beats per minute, blood pressure of 132/92mmHg and respiratory rate of 18 breaths per minute. His lungs clinical examination was normal and his lower extremities were nonedematous. He had no flushing of the skin. His abdomen was soft with normal bowel sounds and without palpable masses, or rebound tenderness. He had no related family history. Laboratory tests were as follows: total testosterone renin 0.1ng/mL/hour (0.05-0.791ng/mL/hour), aldosterone 194.97pg/mL (59-173.997pg/mL). The 24h urine values of vanillylmandelic acid (VMA) and homovanillic acid (HVA) were not elevated: 2.60mg/24h and 2.3mg/24h (2-18years old, <5.0mg/24h). Cortisol compound F

at 4pm was elevated to 345.30nmol/L (<276.4). Plain and enhanced computerized tomography (CT) showed a 55×46 cm round mass at the left adrenal gland with edge enhancement and central necrosis (Figure 2a-2b). These findings were compatible with a PCC. Paraganglioma was suspected given his slight hypertension, the ultrasound and CT imaging findings. Fluorine-18-FDG PET showed intense uptake in left adrenal area with maximum standardized uptake values (SUVmax 32.9) and central ¹⁸F-FDG uptake defect, (Figure 3).

His blood pressure remained stable during the following 10 days before operation (130-134/90-92mmHg). The patient had no clinical signs of catecholamine release, and this tumor was considered biologically inactive. Therefore, no preoperative α -adrenergic blockade was done, and the patient remained hemodynamically stable throughout surgery. Subsequently, left adrenalectomy was successfully performed. There were no complications related to surgery. Histopathologic analyses and immunohistochemical staining were performed and revealed massive necrosis in the tumor and large cells with eosinophilic cytoplasm positive for synaptophysin, S-100 and chromogranin, suggestive of PGL (Figure 4a-c). Following resection, the patient remained normotensive and was discharged after 9 days. He was free from relapse 3 years later as examined recently.



Figure 1. Abdomen ultrasound showed a left retroperitoneal mass.

Discussion

Pheochromocytomas and PGL are rare neuroendocrine tumors that arise from sympathetic and parasympathetic paraganglia [1]. Approximately 10%-20% of all PCC/PGL are diagnosed in children with an average age at diagnosis of 11 years [7, 8]. Our patient was 10 years old. Cases as young as 5 years with PGL were also reported [9, 10]. There is a male predominance of 2:1 including adolescents [3]. Compared to adults, pediatric PCC/PGL are more frequently familial, bilateral, multifocal and malignant [1]. The frequency of bilateral tumors in children is twice as high as in adults (20% versus 5%-10%) [3]. Paragangliomas are highly vascularized tumors as showed by the enhanced mass in our case and can affect any part of the body, most commonly occurring in the carotid body, the jugular tissue, and in the spine [11]. Parang-

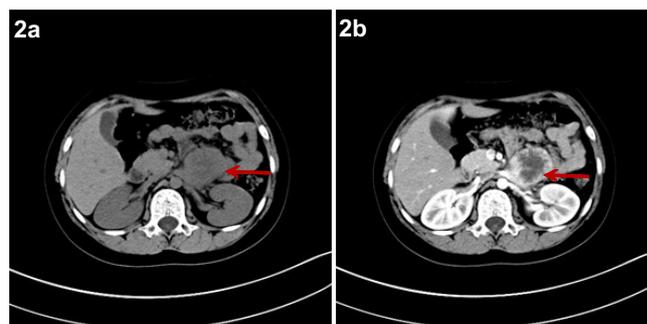


Figure 2. Plain (2a) and enhanced computerized tomography (CT) demonstrated a 55×46cm round mass at the left adrenal gland with central necrosis and edge enhancement (2b).

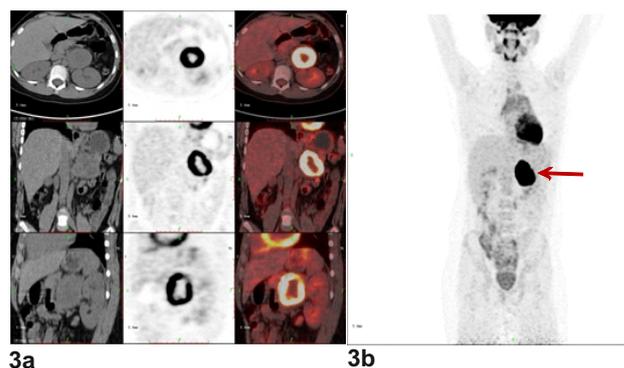


Figure 3. Fluorine-18-FDG PET/CT at horizontal, coronal and sagittal planes (3a) and maximum intensity projection (MIP) image (3b) revealed intense uptake in the left adrenal area with maximum standardized uptake values (SUVmax : 32.9) and a central ¹⁸F-FDG uptake defect.

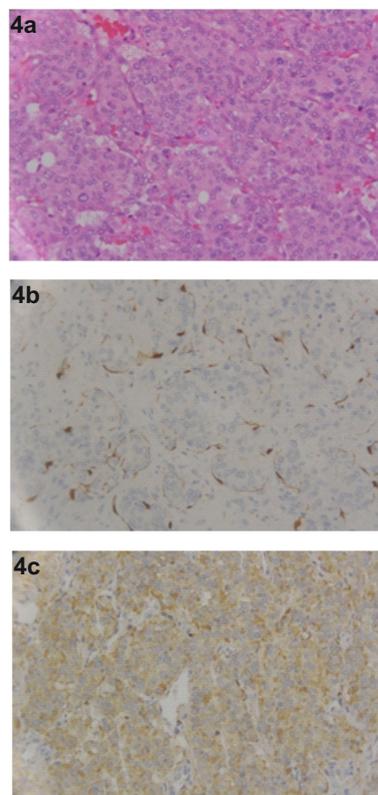


Figure 4. Histopathology and immunohistochemical staining revealed large cells with eosinophilic cytoplasm, was positive for synaptophysin (4a), S-100 (4b) and chromogranin (4c), suggestive of PGL with low-grade malignancy.

liomas located in the head and neck are more often parasympathetic and nonsecretory, whereas PGL within the abdomen are more likely to be sympathetic and associated with catecholamine secretion [4, 12, 13]. Our case had a PGL in the abdomen with mild hypertension but normal serum and urine catecholamine. Hypertension secondary to secretion of adrenaline and noradrenaline is found more frequently in pediatric patients, accounting for 60% to 90% of the cases as opposed to 50% in adults [7].

Approximately 50% of pediatric PCC/PGL cases are associated with a mutation of one of the 12 known susceptibility genes [1]. Genetic testing should be considered for pediatric patients with PGL [15], even having no familial history. It has been reported that over half of all PCC and PGL in patients <18 years old are associated with a germline mutation and that this percentage seems to increase with decreasing age at diagnosis [14]. A 6 years old Japanese girl had convulsions and hypertension and was diagnosed by pathology as an extra-adrenal PGL. Germline mutations in the succinate dehydrogenase complex subunit B (SDHB) gene were also found [15]. A 11 years old boy with SDHB-associated PGL was also reported but without ^{18}F -FDG PET/CT examination [4]. Most sporadic cases of PGL with SDHB mutations occur between adolescence and adulthood [15].

The diagnosis of PGL is first based in biochemical evaluation followed by anatomic imaging and/or functional imaging and surgical pathology. In the pediatric population, elevated plasma-free and fractionated metanephrine have a high sensitivity close to 100% and a specificity of 95% [3]. The metanephrine test was not performed in our case. A concentration of plasma-free metanephrine greater than four times the standard was uniformly associated with the presence of a tumor [16]. Vanillylmandelic acid assay is not recommended because of poor sensitivity [12] as showed by the negative VMA in our case. Anatomic imaging includes ultrasound, CT and magnetic resonance imaging (MRI), while functional imaging includes metaiodobenzylguanidine (MIBG) and octreotide scintigraphy in identifying PGL [1]. A heterogeneous, hypervascular mass with different enhancement indicates areas of necrosis arising from the retroperitoneum in a contrast-enhanced abdominal CT which is highly predictive of PGL [9] as shown in our case. Magnetic resonance imaging is useful as initial radiological approach [1]. Functional imaging providing whole-body scan plays a crucial role in the detection, follow-up, and prediction of possible radioactive treatment options for PGL [17]. The overexpression of somatostatin receptors (SSTR) and adrenergic receptor [18] enables MIBG and octreotide scintigraphy to detect PGL. Gallium-68-DOTATATE PET/CT has a higher sensitivity and diagnostic value in the localization of SDH-related and sporadic head and neck PGL [19]. A comparison study indicated the superiority of 18F-hydroxyphenylalanine (DOPA) PET/CT over iodine-123(^{123}I)-MIBG single photon emission tomography (SPET)/CT to assess disease extension in 12 patients with recurrent PGL ranging from 27 to 70 years [20]. However, in cases of inoperable disease, ^{123}I -MIBG maintains a unique role in allowing the selection of patients suitable for therapy [20].

Fluorine-18-FDG PET/CT has been proven to be a highly sensitive method for PGL associated with succinate dehydrogenase (SDH) mutations [2]. Pheochromocytomas/PGL belonging to the cluster 1 exhibit increased ^{18}F -FDG uptake on PET/CT, compared with cluster 2 tumors [21]. It is not clear, though, whether ^{18}F -FDG-PET provides independent information on whether an adrenal mass is malignant [22]. As shown in our case, ^{18}F -FDG PET is a highly sensitive method to detect PGL, but could not make a differential diagnosis between PGL and PCC, although high uptake of ^{18}F -FDG may indicate malignancy. Fluorine-18-FDG PET/CT avidity does not provide prognostic information in PGL, and SDHx tumors and may have an indolent course, even with highly elevated uptake values of ^{18}F -FDG [22]. Although our case had intense uptake of ^{18}F -FDG in PGL, the boy had no relapse after 3 years of follow-up. There is a poor correlation between tumor SUV and tumor size for both benign and malignant adrenal masses [22]. 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT), a PET proliferation tracer was also compared with ^{18}F -FDG PET/CT in 12 adult patients with PCC/PGL. Fluorine- ^{18}F -FLT showed no apparent superiority, and should not be used for PGL grading or in the evaluation of treatment response [2].

After establishing whether PGL is hormonally active, the next critical question is whether it is benign or malignant [23]. At the present time, there are no reliable cytologic, histologic, immunohistochemical, molecular, or imaging criteria for determining malignancy of PGL [23]. The diagnosis of malignancy remains strictly based on finding metastases in areas where paraganglial cells are not usually present, such as the lymph nodes, lung, bone, or liver [2]. Small tumor size and anatomical imaging characteristics such as unenhanced CT attenuation <10HU (Hounsfield units) and drop of signals on out-of-phase MRI imaging are highly predictive of the benign nature of an adrenal mass [24]. Malignant PGL is defined by the presence of this tumor at sites where chromaffin cells are usually not found or by local invasion of the primary tumor [3]. In the pediatric population, about 12% of PGL are malignant [7]. Recurrence, either regional or metastatic, usually occurs within 5 years of the initial complete resection but long-term recurrences are also described. Malignancy is often linked to a SDHB mutation [3]. Some features such as central necrosis, high mitotic index, large size (greater than 5cm), capsular rupture, or vascular invasion suggest malignancy [3]. Therefore, anatomic and functional imaging play a central role in ruling out metastases but are still limited in that they cannot provide further information about the potential behavior (e.g., malignant potential, proliferation rate, degree of apoptosis, and hypoxia) of these tumors that is closely linked to their genotype, biochemical properties, and localization. The malignancy risk for PCC/PGL has been estimated to be 10%, with an increased risk in sympathetic PGL belonging to the cluster 1 subgroup [2]. Our case had 55cm mass, central necrosis and highly vascularized edge which indicated malignancy established by pathology.

Surgical resection is the mainstay of secretory PCC/PGL but a multimodal approach is often required due to the complexity of pediatric cases. Preoperative medical manage-

ment of hypertension is equally important to ensure good clinical outcomes. The role of preoperative embolization is not established, provides little benefit to diagnosis and has major complications [3]. Treatment should be initiated 1-2 weeks prior to resection to avoid complications from intraoperative catecholamine surges [8, 10, 25]. Furthermore, 1-2 days preoperatively, α -blockade drugs should be stopped and patients may be salt loaded to avoid postoperative hypotension. Surgical resection is most commonly achieved laparoscopically, but in cases of large tumors in concern for malignancy laparotomy may be indicated [4, 12, 26]. As neither signs nor symptoms of catecholamine release were observed in both cases prior to surgery and during biopsy, no α -adrenergic blockade was used and no systemic repercussions were observed in our case. The overall prognosis for tumors with complete surgical resection is excellent [10]. Currently, the use of ^{123}I -MIBG therapy seems to be the most effective treatment in adults. This treatment is complex and requires a number of prerequisites such as hematopoietic stem cells availability. Treatment with ^{131}I -MIBG is of limited value in pediatrics because of its high radiation burden [27].

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