

Case Report

Rare giant thoracic paraganglioma presenting with emesis in a child: a case report

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Abstract: Objective: Extra-adrenal pheochromocytoma, known as paraganglioma, is located in multiple body regions that are commonly the head and neck region, aorta abdominalis, renal blood vessels, and nearby regions of the inferior mesenteric artery, along the sympathetic chain. It has diversified atypical clinical symptoms, and it is very uncommon for children to have giant thoracic paraganglioma. There are many patients with missed or delayed diagnosis due to a lack of knowledge of extra-adrenal and bilateral adrenal pheochromocytoma. Methods: In this paper, we analyzed and summarized the clinical data, diagnosis and treatment of a child with the onset of digestive tract symptoms such as emesis and surgically confirmed giant thoracic paraganglioma who was admitted to the Department of Pediatrics of West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital in October 2016. Conclusion: Pheochromocytoma has diversified clinical manifestations and locations, so careful inquiry of medical history and physical examination combined with imageological and laboratory examinations are important for a definitive diagnosis.

Keywords: Paraganglioma, ectopic pheochromocytoma, emesis, thoracic cavity, mediastinum, children

Introduction

Paraganglioma is a rare neuroendocrine tumor that mainly synthesizes and secretes a large quantity of catecholamine, causing a series of clinical syndromes such as the elevation of blood pressure, and serious complications related to the heart, brain and kidneys. Paraganglioma usually occurs in young adults and is rare in children. Morbidity of paraganglioma is 1.7% in children with hypertension and about 5% in children with adrenal incidentaloma [1, 2]. It can occur at any age in childhood, commonly between 6-14 years old, slightly more in boys than in girls, as a ratio of 3:2 [3, 4]. Unlike adrenal medulla pheochromocytoma, paraganglioma occurs in the extra-adrenal sympathetic chain that is the paravertebral sympathetic chain along the thorax, abdomen and pelvic cavity, as well as in parasympathetic ganglia of glossopharyngeum and vagus nerve distributed along the neck and skull base, and most

commonly in the ganglion-rich region adjacent to the aorta abdominalis and bladder wall of distal ureter. However, it is very uncommon for children to have giant paraganglioma in the thoracic cavity, with the diameter of tumor of more than 8 cm. It has been reported that thoracic paraganglioma accounts for less than 2% of total pheochromocytoma and less than 1% of mediastinal tumors [5]. In particular, there are few reports in children with thoracic paraganglioma due to latent clinical manifestations and difficult diagnosis. In this paper, we reported the clinical data of giant thoracic paraganglioma presenting with digestive tract symptoms such as emesis in a child who was admitted to West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital in October 2016, and reviewed the relevant literature in order to give rise to everyone's vigilance and avoid clinically delayed and missed diagnoses.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital, and informed consent was obtained from the patient for participation in the study. The male child, at 9 years and 4 months, was admitted to West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital in October 2016 for repeated vomiting for more than 6 months. Diagnosis and treatment: The child had repeatedly vomited without apparent cause for more than 6 months before admission and had been treated in other hospitals. The vomituses were gastric contents. Vomiting was non-projectile, which apparently occurred after meals and strenuous exercise, approximately twice a day. Occasional headaches (unspecific nature and location of the headache) could last for about 1 h and be relieved by itself. The results of gastroscopy showed a superficial gastritis. The child was repeatedly treated in the Department of Gastroenterology and took oral drugs for the consideration of gastritis and dyspepsia. However, there was no significant relief from vomiting. The child had no abdominal pain, abdominal distension, cough nor shortness of breath. More than 10 days before admission, the child had repeatedly vomited and was treated in other hospitals again. There was no relief from vomiting after oral administration. After a comprehensive physical examination, a "mass shadow" was found by chest computed tomography (CT), and then the child visited West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital for treatment. Physical examination showed heart rate of 140 beats per minute, respiratory rate at 27 times per minute, and blood pressure of 150/96 mmHg with the highest of 210/170 mmHg, as well as paroxysmal profuse sweating.

Results of auxiliary examinations: 1). Hormone levels: blood norepinephrine 23231 ng/L (272-559), adrenaline 121 ng/L (54-122), plasma renin (clinostatism) >12 ng/mL (0.05-0.79), plasma renin (vertical position) >12 ng/mL (0.93-6.56), angiotensin II (clinostatism) 132.26 ng/L (28.2-52.2), angiotensin II (vertical position) 255.66 ng/L (55.3-115.3), aldosterone (clino-

statism) 21.73 ng/dL (4.5-17.5), aldosterone (vertical position) 33.92 ng/dL (9.8-27.5), dopamine (urine) 1,807.10 ug/24 h (107.2-248.6), norepinephrine (urine) 2,983.72 ug/24 h (16.3-41.5), adrenaline (urine) 13.24 ug/24 h (7.5-21.9), 24 h urine volume of 1.6 L, urine vanillylmandelic acid 208.38 umol/24 h (5.05-25.25 umol, equivalent to 1-5 mg), and normal thyroid function. 2). Routine blood and biochemical detection: Normal blood results, hepatorenal function, electrolyte, blood lipid and coagulation function. 3). Chest and abdominal CT: A space-occupying lesion in posterior lower mediastinum (about at the level of the 7th-10th thoracic vertebra) with regular shape and a large section of about 4.8*6.8 cm. The lesion was an inhomogeneous density and presented a significantly uneven enhancement by enhancement scan. There was liquefaction necrosis in the lesion, and bone destruction near the centrum of the 9th thoracic vertebra and the capitulum of the rib. There was no dilatation of foramen intervertebrale, or intraspinal invasion. Therefore, the lesion might be a neurogenic tumor, and the possibility of other diseases would be investigated. There were no enlarged lymph nodes near the hilus pulmonis, mediastinum and aorta abdominalis after enhancement, pleural effusion and ascites, nor abnormalities in the gall bladder, spleen, pancreas and kidneys. There was a strip of calcified shadow in the upper segment of the right anterior lobe of the liver (**Figure 1**). 4). Fundus examination: Hypertensive retinopathy of the left eye.

Gene detection

With the informed consent of the child's family, 5 mL of venous blood was collected from the child and his parents, and anticoagulated by EDTA; gene analysis was performed. Peripheral blood genomic DNA was extracted and PCR amplification was carried out by using second-generation sequencing and first-generation verification technologies. PE 100 sequencing was performed by using the Hiseq 2500 high-throughput mode. Compared with the standard sequence, the results showed a heterozygous mutation in the RET gene of the child, chr-10:43606832, c.1441C>G(E7). The data in the human gene mutation database showed that RET gene was a dominant inheritance, which could cause pheochromocytoma. Sanger sequencing verification for the child and his parents revealed that his mother carried the same

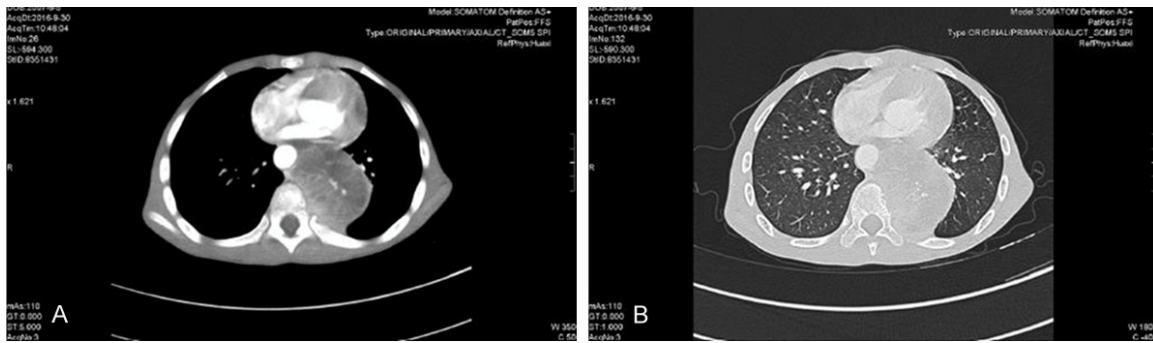


Figure 1. Chest CT. A. Chest CT at mediastinal window; B. Chest CT at lung window.

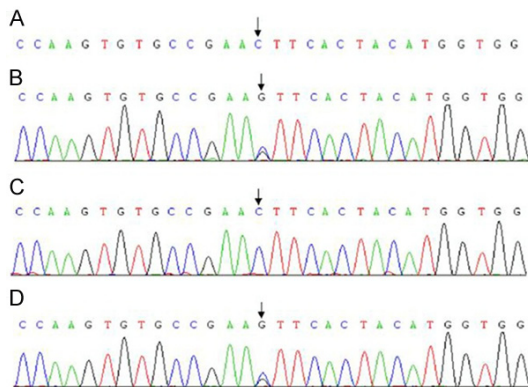


Figure 2. RET gene sequence of the child and his parents. A. National Center for Biotechnology Information reference sequences; B. Heterozygous mutation in RET gene c.1441C>G(E7) of the child; C. No mutation in RET gene of the child's father; D. Heterozygous mutation in the RET gene c.1441C>G(E7) of the child's mother.

missense mutation as the child, indicating that the mutation of the child originated from his mother (**Figure 2**).

Treatment

After admission, phentolamine was given by intravenous infusion, and captopril, prazosin and phenoxybenzamine were administered orally. A surgery was performed at West China Hospital, Sichuan University on October 31, 2016 after blood pressure was controlled. Intraoperative findings: There were many sarciniform adhesions throughout the pleura in the left thoracic cavity, and a large mass in the posterior mediastinum with a diameter of about 8 cm. The firm mass had unclear boundaries with the surrounding tissues and a rich blood supply and invaded the vertebral column and walls of the chest. The surgically resected sam-

ple was diagnosed pathologically as posterior mediastinal paraganglioma. The results of immunohistochemical staining showed positive Syna staining, positive CgA, negative S100, and negative PCK, and the positive rate of Ki67 (MIB-1) of about 2%-5% (**Figure 3**). On the 2nd postoperative day, norepinephrine level was 4,686 ng/L (272-559), and adrenaline was 236 ng/L (54-122) in the peripheral blood. On the 4th postoperative day, norepinephrine was 321 ng/L (272-559), and adrenaline was 76 ng/L (54-122) in the peripheral blood. After surgery, blood pressure dropped to the normal level, and emesis, headache, and profuse sweating disappeared. Outpatient follow-up has been carried out since the surgery. The chest CT was reexamined every six months, and there was no tumor recurrence or metastasis. There were normal blood pressure, blood norepinephrine and adrenaline.

Discussion

Overweight and obesity are the main causes of hypertension in children, and secondary hypertension caused by pheochromocytoma accounts for only 0.1%-0.6% of children's hypertension [6]. Associated with abnormal secretion of large amounts of catecholamines, such as norepinephrine, adrenaline and dopamine, the typical clinical manifestations of extra-adrenal paraganglioma are hypertension, and triad syndromes of headache, profuse sweating and tachycardia caused by sympathetic nervous excitement. Although extra-adrenal paraganglioma is a rare disease, it should be considered when exploring the causes of childhood secondary hypertension and unexplained headaches, profuse sweating, and paroxysmal ochrodermia [7]. In addition to the

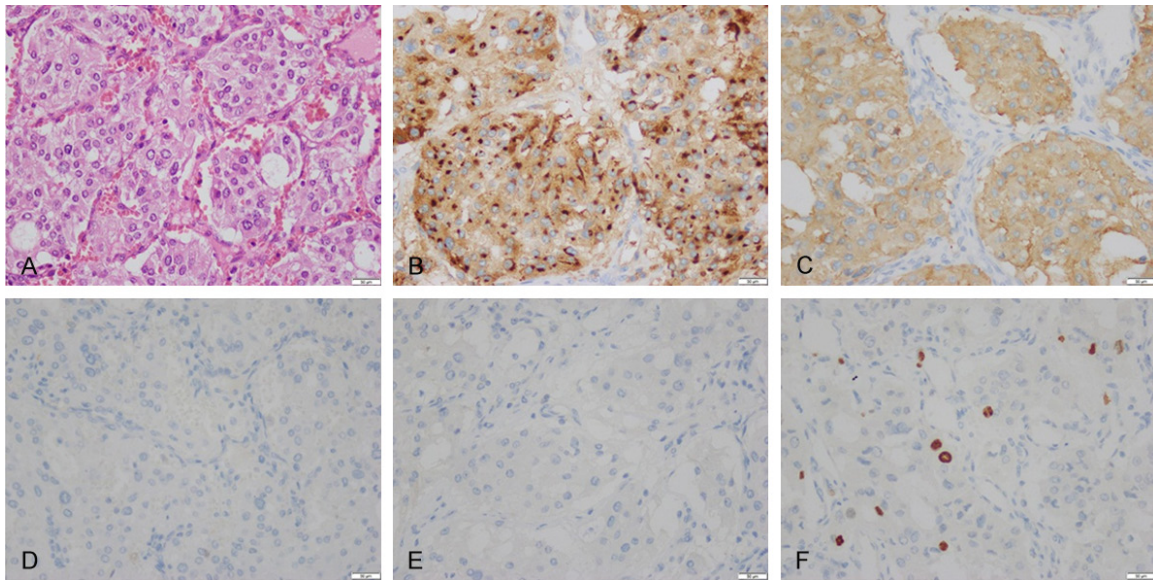


Figure 3. H&E and immunohistochemical staining detection of tumor tissue sections. Tumor cells were arranged in pseudo-acinariform, sarciniform and trabecular shapes, with abundant blood vessels and blood sinus dilatation and hyperemia. The tumor cells had abundant cytoplasm and were eosinophilic and granular with slightly deviated round or oval nucleoli. Most nuclei had loose chromatin and visible nucleoli. Some tumor cells had a certain degree of atypia, and there was occasional hematoxylin-eosin staining mass in mitotic figures at 400× (A) The results of immunohistochemical staining showed positive CgA (B) positive Syna (C) negative S100 (D) negative PCK (E) positive rate of Ki67 (MIB-1) (F) of about 2%-5% in tumor cells. Scale bar=100 mm.

typical triad syndrome, extra-adrenal paraganglioma has diversified clinical manifestations, and many of them are atypical symptoms. Therefore, it is easy to make a misdiagnosis. Severe hypertension can lead to fundus lesions (papilledema, optic atrophy, and fundus exudation) causing visual deterioration, which is the main reason for children's first visit to the hospital [4]. Therefore, children with non-refractive visual impairment should be wary of extra-adrenal paraganglioma. It is also reported that extra-adrenal paraganglioma begins with the symptoms of digestive tract bleeding, fever, and bladder pain after urination [8]. In this report, the child was attacked by digestive tract symptoms with the initial symptom of repeated vomiting but without headache, so the child was misdiagnosed with gastrointestinal disease, having ineffective repeated treatments. Because a mass was found with chest CT, the child visited our hospital for treatment. Physical examination showed hypertension, tachycardia, profuse sweating, and hypertensive retinopathy of the left eye, considering the possibility of extra-adrenal paraganglioma. In addition to catecholamines, pheochromocytoma can also produce a variety of peptide hormones, leading to various atypical symptoms [3, 9, 10]. In this report, vomiting of the child might be caused by cate-

cholamines, vasoactive intestinal peptides, serotonin, and motilin secreted by tumors. Complete surgical resection is the fundamental method for the treatment of paraganglioma.

There was a heterozygous mutation in the RET gene of the child, chr10:43606832, c.1441C>G(E7). This gene mutation was closely related to multiple endocrine neoplasia type 2A. By viewing the medical history, the child's mother and grandfather had hypertension without relevant etiologic examinations, and thus pheochromocytoma of the child might be multiple endocrine neoplasia type 2A caused by RET gene mutation. Outpatient follow-up has been made every six months. Blood pressure, chest CT and blood catecholamine level were reexamined. There was no tumor recurrence or signs of other tumors.

Extra-adrenal paraganglioma was reported to account for about 10%-20% of total pheochromocytoma [10]. It is rare in children with mediastinal paraganglioma. The incidence of extra-adrenal pheochromocytoma is significantly higher in children than in adults (30% vs. 10%) because the chromaffin tissue is more widely distributed and faster developed in children [11, 12]. It was reported that 3% of extra-adre-

A child with thoracic paraganglioma

Table 1. Clinical data of 13 children with special paraganglioma

Report time	Gender	Age (year)	Complains	Primary diagnosis	Diseased region
2018	M	10	Hemoptysis	Obstructive bronchopathy	Primary pulmonary artery [13]
2018	M	8	Wheeze and dyspnea	Asthma	Trachea [14]
2018	M	12	Gross hematuria, vomiting, paroxysmal headaches, polyuria, polydipsia, nocturia, dehydration, and lethargy		8.1 cm*7.5 cm bladder mass on postero-lateral bladder wall [15]
2018	M	10	Abdominal mass, abdominal pain, and fever	Space-occupying lesion in the abdomen	About 5 cm*4 cm*4 cm adjacent to the vertebral column in left posterior peritoneum [16]
2017	F	8	Swollen neck		Carotid body tumor [17]
2016	F	6	Convulsions and hypertension		Paravertebral abdominal tumor [18]
2015	M	3	A large mass on the right side of his neck		(Measured 8 cm*5.5 cm*4.5 cm) carotid bifurcation [19]
2014	M	10	Chest pain and dyspnea	Acute myocardial infarction (acute coronary syndrome)	5.0 cm*2.5 cm in size in the right upper abdomen, near the right adrenal gland region [20]
2014	M	16	Headache, dizziness, and gait disturbance	Slight cerebellar ataxia and bilateral mild optic disc edema	30 mm*26 mm*23 mm solid-cystic lesion in the right cerebellar hemisphere with evident perilesional edema [21]
2014	M	15	Headache		27 mm*17 mm*26 mm in the anterior region of the right renal vein [22]
2013	M	12	Headache, diaphoresis, weakness on the left side of the body, and altered mental status that evolved into a coma	Intracranial hemorrhage	One tumor in the organ of Zuckerkandl, extending from the left renal artery to the aortic bifurcation, dm=9 cm, the other in the right side of the inferior vena cava, dm=2 cm [23]
2013	F	12	Headache and vomiting	Tuberculous meningitis	5 cm*4 cm*5 cm in the bladder [24]
2013	F	12	Dizziness and headache		An enclosed mass of 4.0 cm*4.5 cm between the internal and external right iliac arteries [25]

nal pheochromocytoma in adults occurred in the head and neck, and 85% in the abdomen. However, 50% of extra-adrenal pheochromocytoma in children occurred in the head and neck, and 37% in the retroperitoneum [12]. Compared with adults, familial pheochromocytoma and bilateral pheochromocytoma have a higher incidence of 10% and 24%, respectively, in children. Moreover, pediatric patients account for 15%-32% of all patients with extra-adrenal pheochromocytoma [4]. After the analysis and summary of clinical data of 789 patients hospitalized for pheochromocytoma in West China Hospital, Sichuan University and West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital from January 2009 to January 2018, we found 7 children (3-9-year-old children, 3-14-year-old children, and 1 child under 1 year old) with retroperitoneal adrenal pheochromocytoma, and only 1 child with extremely rare thoracic paraganglioma who was reported in this paper. By using "extra-adrenal", "pheochromocytoma", "paraganglioma", "mediastinum", and "children" in English, and "paraganglioma", "ectopia", "mediastinum" and "children" in Chinese as keywords, we searched the data in Pubmed database, CNKI database, and Wanfang database from January 2013 to November 2018. There were a total of 8 Chinese publications on 3 children with paraganglioma and 0 patients with mediastinal paraganglioma, and 24 foreign publications on 7 patients with extra-adrenal paraganglioma (Table 1).

Ten children reported in Chinese and foreign literature, including 4 females and 6 males, at the minimum age of 3 years old and the maximum age of 16 years old, with most child patients being 6-12 years old. Clinical manifestations were diversified, such as dyspnea, chest pain, hemoptysis, and polyuria, but headache was the main reason for treatment. The tumors involved various locations, and there was no significant correlation between symptoms and the tumor location. In this report, the child's disease began with the gastrointestinal symptoms of repeated vomiting, and the tumor was located in the chest. If there were unclear subjective expression of the child, a lack of detailed observation of parents, and inexperienced physicians, it was very easy to make a misdiagnosis and delay the child's condition.

In conclusion, we should consider the possibility of pheochromocytoma for all children with headaches and hypertension. Due to the diversified clinical manifestations and locations of pheochromocytoma, careful inquiry of medical history and physical examination combined with imageological and laboratory examinations are meaningful for a definitive diagnosis. Due to the onset of pheochromocytoma at a young age, and multiple lesions and recurrent possibility of multiple endocrine neoplasia, close follow-up of the child is necessary in order to detect hypertension, recurrence, and new-onset symptoms in time.

Disclosure of conflict of interest

None.

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