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Pheochromocytoma associated with a succinate dehydrogenase subunit B mutation: A minireview and a case report

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Objective. Pheochromocytomas and paragangliomas are rare neuroendocrine tumors that arise from the chromaffin cells of the adrenal medulla or extra-adrenal tissues. These tumors are characterized by an excessive secretion of catecholamines, which are responsible for the clinical manifestation of the disease. Although most of these tumors are sporadic, underlying genetic abnormalities may be present in up to 24% of the cases. A succinate dehydrogenase subunit B (SDHB) mutation represents one of the rare presentations of the disease. In this study, we represent a rare case of pheochromocytoma associated with SDHB mutation.

Methods. We performed a retrospective review of our case in addition to reviewing the available literature on the same topic.

Results. A 17-year-old patient presented with sustained hypertension. Clinical, laboratory, and radiological evaluations confirmed the diagnosis of catecholamine-secreting tumor. Laparoscopic adrenalectomy was performed. Histopathological and genetic testing confirmed a pheochromocytoma associated with SDHB mutation. No recurrence was detected on two-years of follow up.

Conclusion. Pheochromocytoma associated with SDHB mutation is a rare presentation. Genetic testing for suspecting cases is essential to help to establish the appropriate follow-up plan.

Key words: pheochromocytoma, pediatric, succinate dehydrogenase subunit B mutation, presentation, adrenalectomy

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors that arise from special cells called chromaffin cells, which are present in either the adrenal medulla (in this case called pheochromocytoma - PHEO) or extra-adrenal paraganglionic tissues (in this case called paraganglioma - PGL) (Lenders et al. 2005). The annual incidence of PHEOs/PGLs is between two and eight per million (Chen et al. 2010). It is estimated that up to one-fifth of the cases are detected in the pediatric population (Ciftci et al. 2001). Although most cases of PHEOs/PGLs are benign, malignancy has been reported in up to 15% of pheochromocytoma and in up to 50% of paraganglioma (Pamporaki et al. 2017). Despite most cases of pheochromocytomas are sporadic (Klingler et al. 2001), recent studies reported that about one-fourth of pheochromocytomas are familial and may be associated with underlying genetic syndromes. Of these syndromes, multiple endocrine neoplasia (2A and 2B), succinate dehydrogenase subunit B (SDHB)

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gene mutations, Von-Hippel-Lindau syndrome, and cerebellar hemangio-blastoma are the most commonly involved (Neumann et al. 2002). PHEOs/PGLs are characterized by the secretion of large amounts of catecholamines mainly dopamine, norepinephrine, epinephrine, and others. The high circulating level of catecholamines is responsible for most of the clinical manifestation of these tumors such as hypertension, tachycardia, headaches, sweating, flushing, vomiting, and abnormalities in cardiac conduction (Romero et al. 2015). The most common clinical presentation in children with pheochromocytomas or paragangliomas is hypertension (Sheps et al. 1999).

The diagnosis of pheochromocytoma and paraganglioma is usually challenging. Imaging alone is not sufficient to differentiate between these tumors and other adrenal pathologies. Diagnosis depends mainly on detecting high levels of catecholamines or their metabolites in blood or urine (Klingler et al. 2001). Imaging studies that could be used for localization of these tumors may include ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). ^{131}I-metaiodobezylguanidine radioisotope scan may be required when the previous studies are inconclusive or to detect distant metastasis (Bouloux and Fakehh 1997). Laparoscopic adrenalectomy remains the best management option for patients with PHEOs/PGLs with overall better clinical outcomes when compared with open surgery.

The succinate dehydrogenase (SDH complex) enzyme plays a critical role in the mitochondria as it is linked to two important pathways in energy conversion: the citric acid cycle (Krebs cycle) and oxidative phosphorylation. This enzyme is composed of four protein subunits: SDHA, SDHB, SDHC, and SDHD (Entrez Gene). SDHB subunit plays an intermediate role in SDH enzyme structure and function. It was found that germline mutations in SDHB subunit are associated with an increased risk of PGLs/PHEOs and renal cell carcinoma. The risk of malignancy in SHDB carriers ranges from 38–83% (Neumann et al. 2004; Brouwers et al. 2006). The number of reported cases of pheochromocytoma associated with SDHB mutation in adolescents is limited in the literature (Jochmanova et al. 2017; Huang et al. 2018).

In the current study, we add another case of pheochromocytoma associated with SDHB mutation in an adolescent to the literature. We focused mainly on the clinical presentation, preoperative assessment and management, surgical intervention and the outcomes. In addition, we included a mini-review of the literature.

Table 1
Clinical and laboratory data of patient

Parameter	Results	Reference range
Hemoglobin (g/L)	135	115–160
WBCs ($\times 10^9$/L)	8.4	4–11
Platelets ($\times 10^9$/L)	397	150–400
Na (mmol/L)	143	133–146
K (mmol/L)	3.8	3.5–5.3
Urea (mmol/L)	1.7	2.5–7.8
Creatinine (μmol/L)	38	42–100
PTH (pmol/L)	4.8	1.3–7.3
ACTH (ng/L)	<5	<47
Plasma metanephrines (pmol/L)	148	<510
Plasma normetanephrine (pmol/L)	>25,000	<1180
Plasma 3-methoxytyramine (pmol/L)	532	<180
Calcitonin (ng/L)	4	<6
Cortisol/creatinine ratio (nmol/mmol)	3.5	5–55
Plasma Cortisol (nmol/L)	32	119–618
Chromogranin A (μg/L)	1135	<102
25-OH Cholecalciferol (nmol/L)	26.1	50–75
Aldosterone (pmol/L)	667	103–859

Abbreviations: ACTH – adrenocorticotropic hormone; PTH – parathyroid hormone; WBC – white blood cells.

Case presentation

A 17-year-old female patient admitted to the pediatric ward with a history of repeated vomiting and hypertension. Past medical history included mild learning difficulties and well-controlled asthma on inhalers (steroids and β agonists) with no previous history of pounding aches or palpitations. On clinical review, body mass index (BMI) was 14.4 kg/m^2, blood pressure was 140/112 mmHg, pulse rate was 127 peats/min, hands were cold and clammy to touch, heart sounds were normal and the chest was clear. No marfanoid habitus and evidence of mucosal neuromas were detected. Abdominal examination was unremarkable with no palpable masses.

Investigations

Table 1 below shows the results of the preoperative blood tests done for the diagnosis of the patient's adrenal pathology.

Abdominal CT scan revealed an ill-defined enlarged right adrenal gland measuring approximately 45 mm in diameter with extensive contact and possibly invasion of the posterior wall of the IVC. The right renal vein was just separated and inferior to it. The right renal artery was also probably separated from it. The fat plane was intact between the right adrenal and the liver. No distant metastatic disease was found on CT scan. MRI scan showed a well-circumscribed moderately hyperintense mass arising within the right adrenal gland and indenting the posterior aspect of the retro-hepatic vena cava. The two structures remained sharply demarcated with no evidence of flow disturbance at the point of contact on post-contrast sequences (Figure 1). The case was discussed in an endocrine MDT meeting including surgeon, endocrinologist, pathologist, radiologist, and anesthetist and recommended laparoscopic adrenalectomy. An informed consent has been obtained from the parents before surgery.

Treatments. Treatment was initiated with alpha-adrenergic blocker doxazosin, then switched to alpha adrenergic antagonist phenoxybenzamine. Later beta blockers were added. The patient was submitted to laparoscopic right adrenalectomy through trans-abdominal approach. The tumor was removed showing a nodule measuring 50×30×30 mm weighting 58 g. The tumor was positive with chromogranin and sustentacular cells were positive with S100, but no staining was seen with calretinin or melan A. Histopathological examination confirmed pheochromocytoma with no capsular invasion and extension into the peri-adrenal adipose tissue (Figure 2). The PASS score was 2, which was indicative of a benign course. The features were in keeping with a fully excised pheochromocytoma. Genetic testing confirmed a point mutation at SDHB (c.72+1G>A). The patient recovered very well from the operation and still under our care for follow-up. No recurrence was identified for two years now.

Discussion

Pheochromocytoma (PHEOs) and paragangliomas (PGLs) are rare tumors that develop from the chromaffinn cells, which are present in either the adrenal medulla or other paraganglia in the body (Lenders et al. 2005). PGLs can arise from both the sympathetic and parasympathetic nervous systems. The annual incidence of PHEO/PGLs is between two

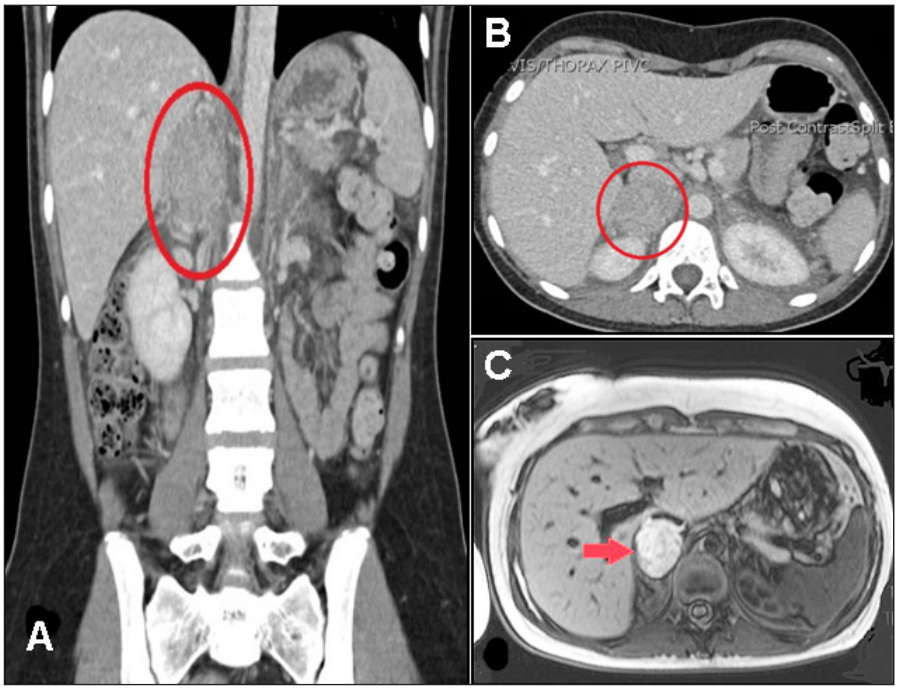


Figure 1. Radiological imaging of abdominal CT scans **(A, B)** showing ill-defined enlarged right adrenal gland measuring appr. 45 mm in diameter. Abdominal MRI scan **(C)** showing a well-circumscribed moderately hyperintense mass arising within the right adrenal gland and indenting but not invading the posterior aspect of the retro hepatic cava.

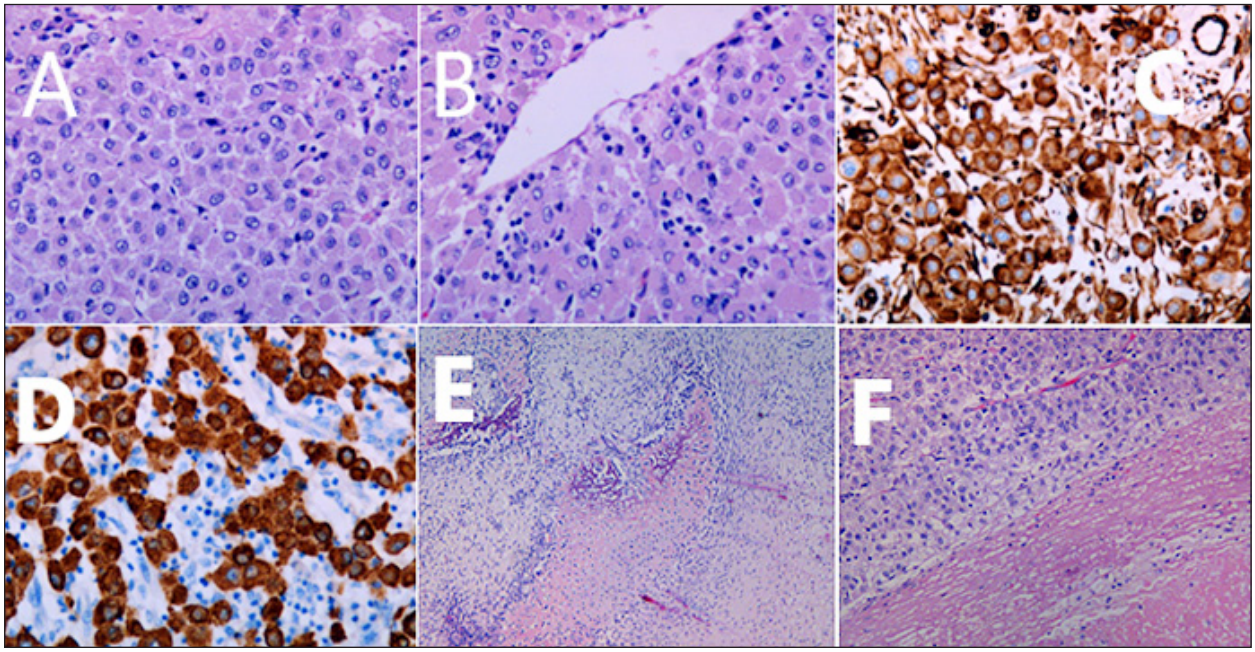


Figure 2. Histopathological demonstration of confirmed pheochromocytoma with no capsular invasion and extension into the peri-adrenal adipose tissue.

and eight per million (Chen et al. 2010). Although more than 80% of the cases are sporadic, it has been found that up to 25% of the PHEOs/PGLs cases might be associated with underlying genetic syndromes such as Von Hippel-Landau (VHL) disease, type 1 neurofibromatosis (NF1), multiple endocrine neoplasia (2A and 2B), succinate dehydrogenase subunit B (SDHB) gene mutations, cerebellar hemangio-blastoma, Sturge-Weber syndrome and tuberous sclerosis (Neumann et al. 2002). Approximately, 10–20% of all PHEOs/PGLs are diagnosed in pediatric population with underlying germline mutations in about 80% of them (Barontini et al. 2006; Choat et al. 2014). The main clinical manifestations of PHEOs/PGLs are related to excess production of catecholamines (norepinephrine, epinephrine, and dopamine). The classical clinical triad includes episodic headache, sweating, and hypertension; however, sustained hypertension without paroxysm has been reported in about 63% of pediatric patients with pheochromocytoma (Armstrong et al. 2008). The main clinical presentation of our case was sustained hypertension. Caty et al. (1990) have reported similar observation.

The detection of increased levels of catecholamines or their metabolites in the blood or urine is usually required to diagnose pheochromocytoma (Klingler et al. 2001). Plasma free metanephrines (metanephrine and normetanephrine) provide the test of choice for the diagnosis of PHEOs/PGLs (Lenders et al. 2002). Plasma normetanephrine levels were significantly elevated in our patient. The most commonly used imaging studies for localization of PHEOs/PGLs include abdominal ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI), ^{123}I-meta-iodo-benzyl-guanidine (MIBG) and 18-fluorodeoxyglucose (18F-FDG) PET-CT (Shimazui et al. 1989). CT and MRI scans have about 95% sensitivity and 70% specificity for detecting adrenal pheochromocytomas (Maurea et al. 1996). Our patient had MRI scan, staging CT, and MIBG scans to exclude any metastasis.

Catecholamines release from PHEOs/PGLs is normally episodic, but if not managed effectively, it can lead to major consequences. As a result, early detection and treatment are critical (Pacak 2007). In general, preoperative medical therapy of hormonally active pheochromocytoma begins with α-blockers followed by β-blockers and appropriate intravascular volume restoration. The most widely preferred α-antagonist for PHEOs is phenoxybenzamine, a nonselective α-antagonist (van der Horst-Schrivers et al. 2006). The initial dose of phenoxybenzamine is 10 mg twice daily and increased by 10–20 mg every third day. The main side effects include reflex tachycardia, sedation, and sustained hypotension due to the long half-life of the drug. Prazosin and doxazosin are

examples of selective α-1 antagonists that can be used with less pronounced side effects. β-blockers should be used only after adequate α-blockade. If β-blockers were used initially without α-blockade, the unopposed α-stimulant action of catecholamines would lead to hypertensive crisis. Examples of β-blockers include metoprolol or propranolol (Crago et al. 1967). Our patient was managed initially with α-blocker followed by β-blocker before surgery.

Laparoscopic adrenalectomy is associated with numerous benefits, including a shorter hospital stay, faster recovery, less postoperative discomfort, and fewer painkiller prescriptions, as well as lower morbidity and death rates (Pedziwiatr et al. 2015). After surgery, most patients develop normotension without the need for antihypertensive medications, with normalization of serum metanephrines levels. Our patient had successful laparoscopic adrenalectomy with no major complications and restoration of the normotension status postoperatively without the need for any more antihypertensive medications. In addition, the plasma levels of metanephrines and chromogranin A have returned to the normal ranges after surgery.

We know that the main function of succinate dehydrogenase (SDH or Complex II) protein complex is to catalyze the oxidation of succinate (succinate + ubiquinone => fumarate + ubiquinol). SDH is required for the conversion of food energy into a form that cells can use. SDHA, SDHB, SDHC, and SDHD are the four protein subunits that make up the SDH complex. The gene that codes for the SDHB protein in humans is found at location p36.1-p35 on the first chromosome. The SDHB protein complex is located on the mitochondrial inner membrane (Entrez Gene). It weighs 31.6 kDa and is composed of 280 amino acids (Zong et al. 2013). It is located between SDHA, on one end of the enzyme and the two transmembrane subunits SDHC and SDHD, on the other end (Sun et al. 2005). SDHB mutations are known to increase the risk of PGLs/PHEOs and renal cell carcinoma (Ricketts et al. 2008).

The precise pathway from SDHB gene mutation to tumor formation is unknown; however, various theories exist, including the creation of reactive oxygen species, the accumulation of succinate in the cytosol, and impaired developmental apoptosis (Gottlieb and Tomlinson 2005). Mutations in SDHB are usually inherited in an autosomal dominant manner (Neumann et al. 2018). The development of tumor in these circumstances usually follows the Knudson "two hit" hypothesis where the first copy of the gene is mutated in all cells. The second copy continues to function normally until an event happens that could cause a mutation in a certain cell. As a result, loss of heterozygosity (LOH) develops, resulting in aberrant protein production and tumor growth (Knudson 1971). The majority of PHEOs/PGLs associated with SDHB mutations in children develop throughout adolescence. Patients with SDHB mutations have a lifetime risk of 77–100% developing PGL/PHEOs and a 10–20% chance of developing renal cell carcinoma (Bausch et al. 2014). It is critical to conduct genetic testing for patients with PHEOs/PGLs who are suspected of carrying SDHB mutations in order to determine, of which cancers they are at risk, develop an appropriate surveillance plan for them, and provide genetic testing of other family members.

SDHB mutations are associated with a more aggressive disease despite the fact that children with PHEOs/PGLs have a better overall prognosis (King et al. 2011; King and Pacak 2014). According to the European Society of Endocrinology, all patients with PHEOs/PGLs should have frequent post-operative follow-up for at least 10 years, and individuals at high risk of recurrence, particularly young patients, patients with big tumor masses, and those with a genetic condition, should have lifelong follow-up (Plouin et al. 2016). However, there are no universal guidelines for the surveillance of patients with SDHB mutations. SDHB genetic testing is also advised for all first-degree relatives (Wong et al. 2019). As a result, our patient undergoes regular clinical follow-up accompanied by plasma chromogranin A and metanephrines testing along with yearly CT scan to identify any recurrent disease or any new primary elsewhere.

Conclusion

Pheochromocytomas and paragangliomas are rare catecholamine secreting tumors. SDHB mutation was associated with aggressive form of the disease with an early age of onset, larger tumor and high rate of recurrent/metastatic disease. Genetic testing for suspecting cases is essential to help to establish the appropriate follow-up plan. Genetic evaluation for family members of SDHB mutations carriers is also recommended. As most of the available data are reported as case reports, our knowledge regarding SDHB mutation and the association with PHEOs/PGLs is still limited and more researches are still required.

Conflicts of interest: *Authors declare no conflict of interest.*

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