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Case Report

CASE REPORT

Paradoxical hypertension

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by white matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain predominantly. A 48-year-old female patient presented to ER with complaints of breathlessness and developed sudden painless loss of vision while eliciting history. The patient had a heart rate of 104/min and accelerated hypertension (BP of 220/120 mm of Hg). MRI Brain showed subcortical white matter T2/Fluid-attenuated inversion recovery hyperintensities, suggestive of PRES. The patient regained vision completely over 5 days after nitroglycerin infusion and calcium channel blockers. Beta blocker was started in view of increased BP and anxiety. Blood pressure paradoxically increased from 170/90 mm of Hg to 200/100 mm of Hg. Urine and plasma metanephrines were elevated. Contrast-enhanced computerized tomography abdomen showed locally infiltrative, retroperitoneal mass in left para-aortic prevertebral region diagnosed as paraganglioma. The patient improved with alpha blockers and surgical removal of paraganglioma. 0.1% of hypertensive patients harbor a pheochromocytoma or paraganglioma and its presentation as PRES is very rare.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by symptoms including a headache, seizures, altered consciousness and visual disturbances [1]. PRES was first described by Hinchey *et al.* [2]. Shortly after the description in 1996, two other case-series were published [3]. This condition has been known by various names previously (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome and reversible occipital parietal encephalopathy). PRES is now the widely accepted term [4]. It is commonly, but not always associated with acute hypertension [1].

The major clinical conditions associated with PRES are represented in Table 1. There is wide variation in the severity of clinical symptoms, i.e. the visual disturbance can vary from blurred vision, homonymous hemianopsia to cortical blindness. Altered consciousness may vary from mild confusion or agitation to coma. Other symptoms include nausea, vomiting and brainstem deficits. Seizures and status epilepticus are common, while non-convulsive status epilepticus may be common than generalized status epilepticus.

Paragangliomas are very rare neuroendocrine tumors that originate from the extra-adrenal autonomic paraganglia, derived from the embryonic neural crest and have the ability to produce catecholamines. As the clinical patterns of paraganglioma are described usually together with those of pheochromocytoma, the specific incidence of paraganglioma is not clearly known. The combined estimated annual incidence of pheochromocytoma/paraganglioma is ~0.8 per 100 000 person-years [5].

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Pheochromocytomas and paragangliomas occurrence is ~0.05–0.1% of patients with sustained hypertension. However, this only accounts for ~50% of people, as another half of patients with pheochromocytoma or paraganglioma have paroxysmal hypertension or normotension. The prevalence can be estimated to lie between 1:6500 and 1:2500 with the annual incidence in the USA of 500 to 1600 cases per year [6].

Table 1: PRES-associated clinical conditions

Pre-eclampsia (6%)
Eclampsia (6%)
Infection/Sepsis/Shock (7%)
Autoimmune disease (45%)
Cytotoxic medications (19%)
Transplantation including bone marrow or stem cell transplantation (0.5–10%)
Hypertension (61%)

CASE REPORT

A 48-year-old female was brought to the emergency room with the history of shortness of breath, headache, and nausea since 3 h. The patient was referred from a local hospital for increased blood pressure (BP). The patient developed sudden painless loss of vision in both eyes while taking history within 10 min of entering the emergency room. No history of hypertension or other comorbidities was found as per previous medical records. No other significant history was available. On examination, the patient had a heart rate of 104/min, BP of 220/120 mm of Hg and basal crepitations. The patient was drowsy but arousable, had normal pupillary reflex, normal extra-ocular movements, normal fundoscopy but, no light perception. There were no signs of meningeal irritation.

Laboratory examination revealed normal hemoglobin (13.5 g/dl), mild leukocytosis (11 300 cells/dl), and elevated C-reactive protein (4.5 mg/dl). ESR, liver function tests and renal function tests were normal. Other blood tests, coagulation profile, autoantibodies and neoplastic markers were normal.

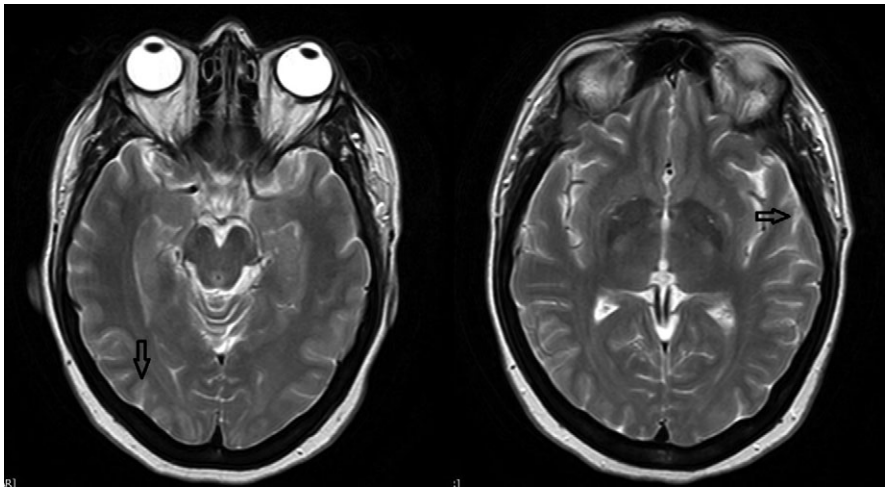

Figure 1: Axial view showing bilateral occipital, parietal and subcortical white matter T2/FLAIR hyperintensities.

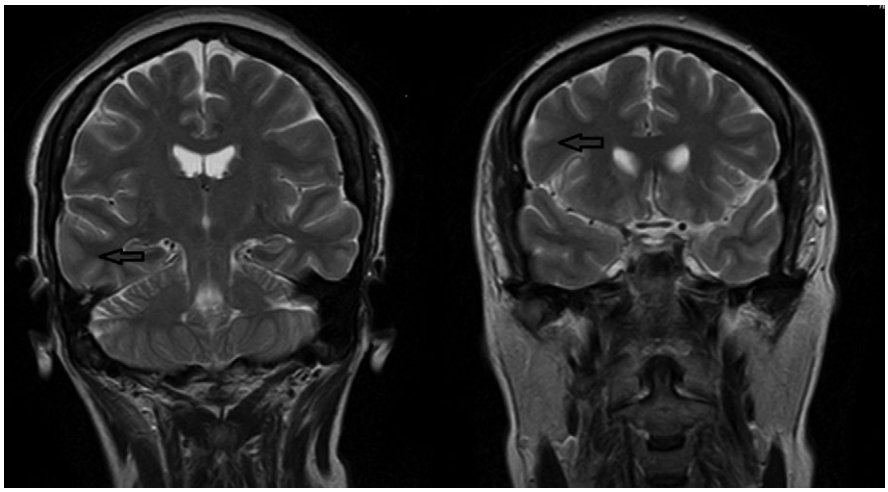

Figure 2: Coronal view of MRI brain showing bilateral occipital, parietal and subcortical white matter hyperintensities.

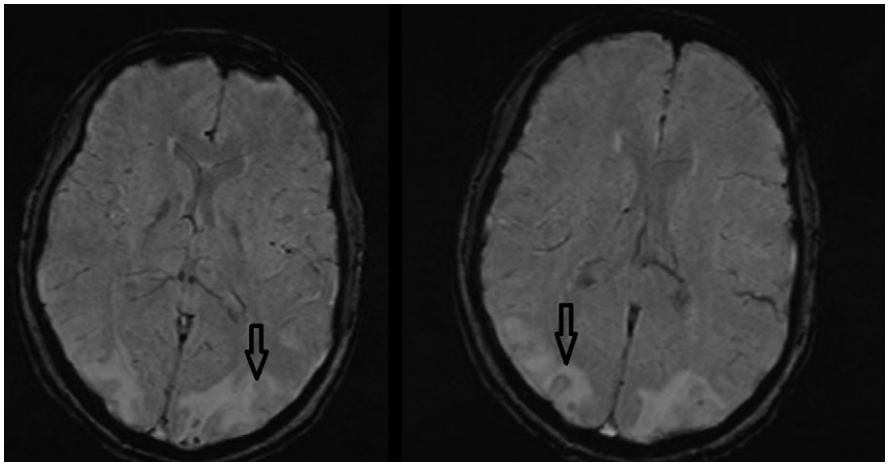

Figure 3: MRI brain showing bilateral occipital, parietal and subcortical white matter hyperintensities.

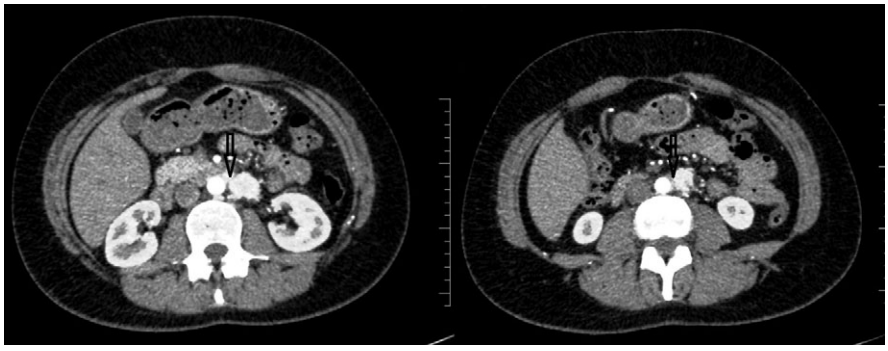

Figure 4: CECT abdomen showing irregularly marginated, locally infiltrative retroperitoneal mass in the left para-aortic prevertebral region.

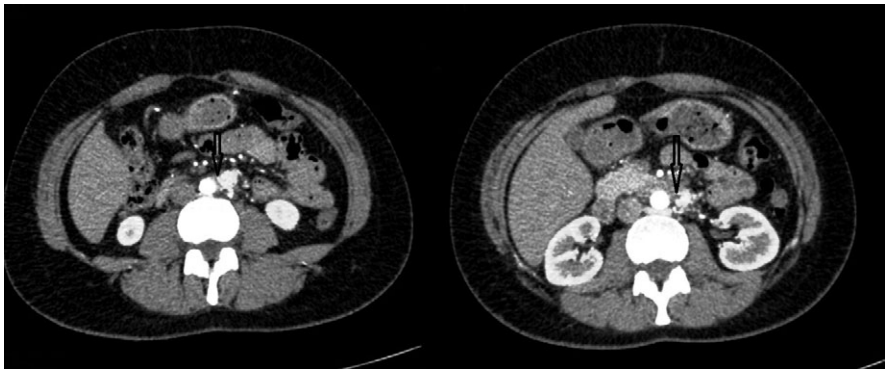

Figure 5: CECT abdomen showing irregularly marginated, locally infiltrative retroperitoneal mass in the left para-aortic prevertebral region.

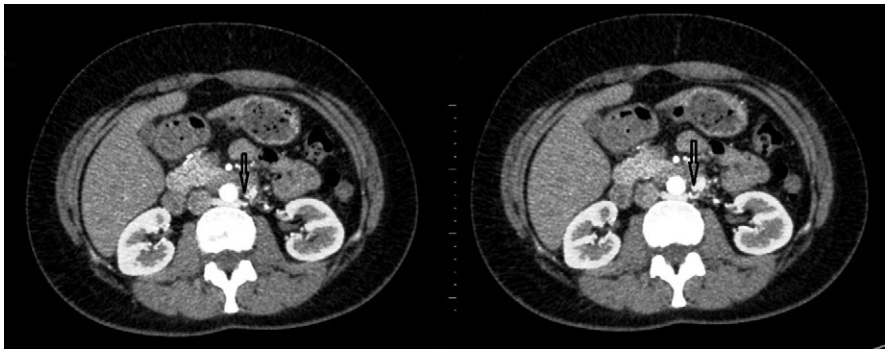

Figure 6: CECT abdomen showing irregularly marginated, locally infiltrative retroperitoneal mass in the left para-aortic prevertebral region.

Cerebrospinal fluid analysis revealed an increase in protein level (55 mg/dl). Chest radiography showed features of pulmonary edema and arterial blood gas analysis was normal. Magnetic resonance imaging brain showed bilateral occipital, parietal and subcortical white matter T2/Fluid-attenuated inversion recovery (FLAIR) hyperintensities (Figs 1–3), suggestive of PRES.

The patient was managed in intensive care unit with nitroglycerin (NTG) infusion, furosemide, calcium channel blockers and telmisartan. Lipid profile and thyroid profile was normal. Electroencephalography showed diffuse theta/delta slowing, bilateral temporal–occipital epileptiform discharges. Electrocardiogram and echocardiogram were normal. Ultrasound abdomen, renal artery doppler and neck vessel doppler were normal. The patient improved symptomatically in form of reduced shortness of breath and regaining vision completely over a period of 5 days. On Day 4 BP of patient was 160/90 mmHg on Telmisartan 40 mg once daily, Cilnidipine 10 mg bis in die (two times a day) (BID), and Hydrochlorothiazide 12.5 mg once daily.

Due to persistently high BP and anxiety in the patient, beta blocker Metoprolol 25 mg BID was added on Day 4. BP paradoxically increased to 180/100 mmHg. In view of paradoxical BP increase, further evaluation was done. Serum cortisol, parathormone, calcium, and phosphorus was normal. Urine VMA was normal (5.6 mg/dl), while urine metanephrine (1200 μg/ml) and plasma metanephrine (550 μg/ml) were elevated. Contrast-enhanced computerized tomography (CECT) abdomen showed a $33 \times 23 \times 34\ mm^3$ irregularly marginated, locally infiltrative, retroperitoneal mass in the left para-aortic prevertebral region below the level of left renal hila suggestive of paraganglioma (Figs 4–6).

PET scan showed no evidence of metastasis. The patient was started on α blocker Phenoxybenzamine along with other antihypertensives after which BP normalized. The patient underwent surgical resection of the tumor. Biopsy confirmed the diagnosis of neuroendocrine tumor, i.e. extra-adrenal paraganglioma (Figs 7 and 8). The patient is discharged in a stable condition after 1 week with normal BP.

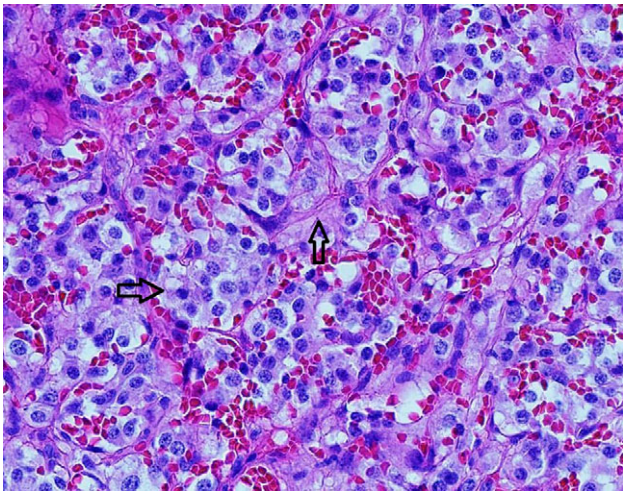

Figure 7: Biopsy showing features of neuroendocrine tumor, pleomorphic tumor cells arranged predominantly in the interconnecting cords, trabeculae and organoid Zell ballen patterns.

DISCUSSION

Paragangliomas arise from either parasympathetic or sympathetic paraganglia. Sympathetic paragangliomas commonly produce catecholamines and are usually present in the paravertebral ganglia of thorax, abdomen and pelvis. Majority of parasympathetic paragangliomas are nonfunctional and are usually found along the glossopharyngeal and vagal nerves in the base of the skull and neck. Catecholamine-secreting paragangliomas present usually like pheochromocytomas with an episodic headache, tachycardia, hypertension and sweating. Common clinical features are described in Table 2 [7].

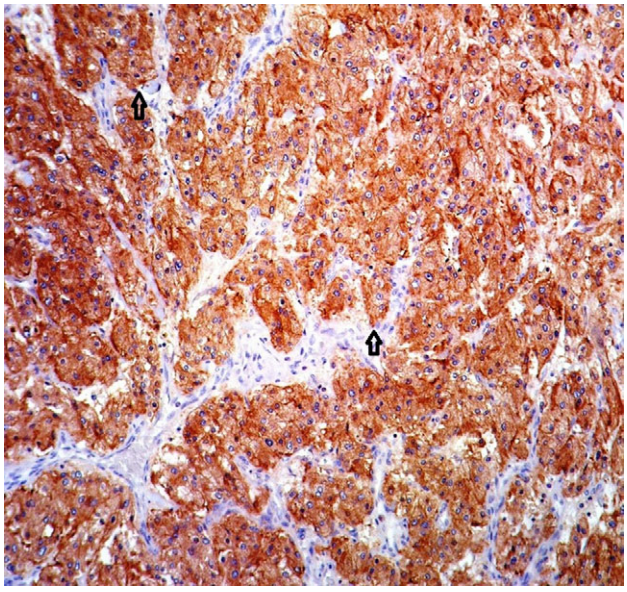

Figure 8: Biopsy with synaptophysin stain showing features of the neuroendocrine tumor.

Table 2: Clinical features of catecholamine-secreting tumors

1. Headaches (51–80%)
2. Profuse sweating (32%)
3. Palpitation and tachycardia (31%)
4. Hypertension, sustained or paroxysmal (50%)
5. Anxiety and panic attacks
6. Pallor (12%)
7. Nausea (4%) [20]
8. Abdominal pain (8%)
9. Weakness (2%)
10. Left ventricular dysfunction (10%) [21]
11. Tinnitus (7%)
12. Weight loss (2%)
13. Paradoxical response to antihypertensive drugs
14. Polyuria and polydipsia
15. Constipation (6%) [22]
16. Orthostatic hypotension (10–50%) [23]
17. Dilated cardiomyopathy (2%) [24]
18. Erythrocytosis
19. Elevated blood sugar
20. Hypercalcemia
21. Pre-eclampsia in pregnancy (1%)

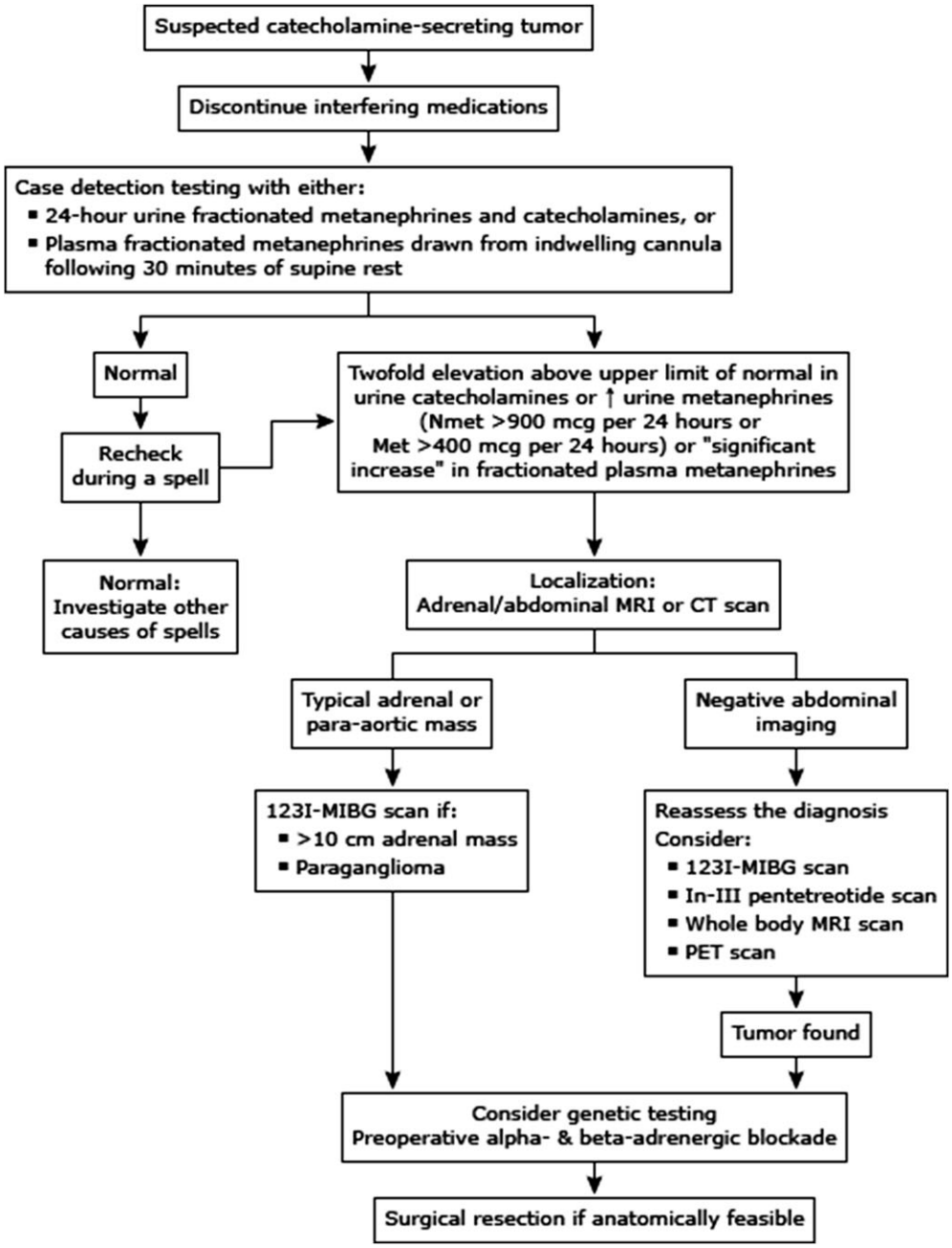

Figure 9: Evaluation and treatment of catecholamine secreting tumors. Nmet, normetanephrine; Met, metanephrine; MRI, magnetic resonance imaging; CT, computed tomography; 123I-MIBG, 123I-meta-iodobenzylguanidine; PET, positron emission tomography.

The differentiation between pheochromocytoma and paraganglioma is an important, as there are implications of associated neoplasms, the risk for malignancy and requirement of genetic testing. Sympathetic paragangliomas can arise from the base of the skull (5%) to the bladder and prostate (10%) [8]. Around 75% arise in the abdomen, 10% in the thorax, including pericardial locations [9, 10]. Sympathetic paragangliomas can also arise from the thyroid gland [11, 12], adjacent to the thoracic spinal cord [13], and at the level of the cauda equina [14].

The majority of paragangliomas are sporadic. Recent studies showed an association with an inherited syndrome in one-third to one-half of patients [15, 16]. Some of the hereditary paragangliomas that are located in the head and neck, have mutations in the genes encoding succinate dehydrogenase (SDH) enzyme complex subunits. Susceptibility to pheochromocytomas/paragangliomas is a well-known component of multiple endocrine neoplasia types 2 A and 2B (MEN2), neurofibromatosis type 1 (NF1), von Hippel Lindau (VHL) and Carney–Stratakis dyad syndromes.

Most paragangliomas occur in age groups of third to fifth decades. The mean age of patients was 47 years in a study of 236 patients at diagnosis with benign paragangliomas [17]. The male to female ratio is equal in hereditary paraganglioma, while sporadic tumors are frequent in women (71 vs. 29 %) [18]. The sporadic paragangliomas that arise in the carotid body are more common in patients living at high altitudes and with a

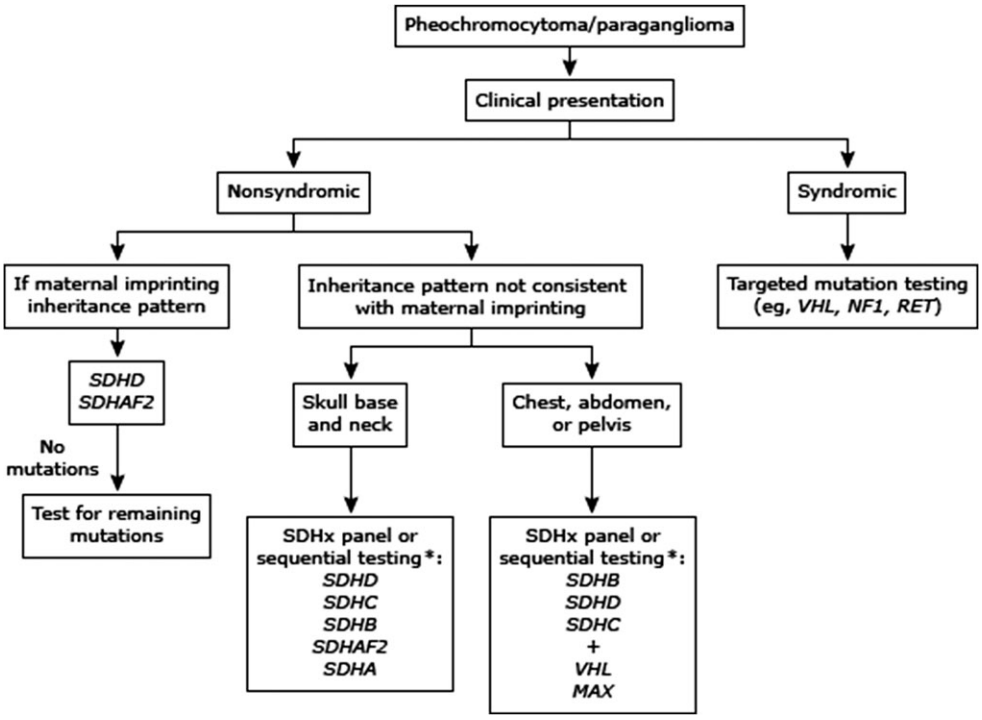

Figure 10: Genetic testing algorithm for patients with pheochromocytoma/paraganglioma. VHL, von Hippel-Lindau gene; NF1, neurofibromatosis type 1 gene; RET, rearranged during transfection gene; SDHD, succinate dehydrogenase subunit D gene; SDHAF2, succinate dehydrogenase complex assembly factor 2 gene; SDHx, succinate dehydrogenase complex genes; SDHC, succinate dehydrogenase subunit C gene; SDHB, succinate dehydrogenase subunit B gene; SDHA, succinate dehydrogenase subunit A gene; MAX, MYC-associated factor X gene.

history of chronic obstructive lung disease with females forming the majority (86–96%) [18]. Evaluation and treatment of catecholamine-secreting tumors are represented in Fig. 9. Genetic testing algorithm for patients with pheochromocytoma/paraganglioma is represented in Fig. 10 [19].

Paragangliomas uncommonly secrete epinephrine, because of the phenylethanolamine *N*-methyltransferase (PNMT) enzyme, that converts norepinephrine to epinephrine, needs cortisol as a cofactor. 24-h urine collection for norepinephrine and fractionated metanephrines is sensitive for paragangliomas compared to epinephrine. Our patient presented with shortness of breath and developed painless loss of vision and was diagnosed with PRES. The patient developed paradoxical hypertension on starting beta blockers, which alerted for further evaluation. Paraganglioma presenting as PRES and paradoxical hypertension is very rare.

Beta-blockade can be administered after starting alpha blockade, if tachycardia or other cardiac arrhythmias develop. Beta blockers must never be administered prior to adequate alpha blockade, since, profound unopposed alpha-mediated vasoconstriction can cause hypertensive crisis or pulmonary edema in the absence of beta-2-mediated vasodilatation.

CONCLUSION

Patient harboring a paraganglioma can present with features of pulmonary edema, hypertension and PRES. Beta blockers should not be administered until adequate alpha blockade has been done, because unopposed alpha-adrenergic receptor stimulation can precipitate a hypertensive crisis. A high index of suspicion and prompt treatment can reduce morbidity, mortality and pave the path for early recovery.

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CONFLICT OF INTEREST STATEMENT

None.

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ETHICAL APPROVAL

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CONSENT

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GUARANTOR

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