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Case Report

A Woman with Bilateral Pheochromocytoma and Tuberous Sclerosis Complex

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ABSTRACT

Background/Objective: Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors. Here, we report an unusual case of synchronous PPGL in an asymptomatic patient with tuberous sclerosis complex (TSC).
Case Report: A 49-year-old woman with a history of TSC and end-stage renal disease was referred for evaluation of bilateral adrenal and retroperitoneal masses. She denied chest pain, palpitations, headaches, or previous hypertensive crisis. The laboratory test results showed a plasma normetanephrine level of 20.20 nmol/L (normal range, 0.00-0.89 nmol/L) and plasma chromogranin A level Chromogranin A (CgA) levels of 1518 ng/mL (normal range, 0-103 ng/mL). The plasma metanephrine level was normal. After α-blockade, the patient underwent bilateral adrenalectomy and retroperitoneal mass excision. Pathology confirmed these lesions to be pheochromocytoma and composite paraganglioma/ganglioneuroma, respectively. Her plasma normetanephrine level normalized postoperatively, and the chromogranin A levels improved to 431 ng/mL.
Discussion: Routine imaging has increased the incidental diagnosis of PPGL. Diagnostic workup includes measurement of the urinary and/or plasma metanephrine and catecholamine levels followed by tumor localization. Patients with young age, syndromic lesions, bilateral PPGL, or unilateral disease with a positive family history should have genetic testing. Definitive treatment is surgical after α-blockade.
Conclusion: This case highlights a rare presentation of bilateral PPGL in a patient with TSC.

Introduction

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors (NETs) derived from neural crest progenitor cells. Pheochromocytoma (PCC) is a tumor of chromaffin cells in adrenal medulla, whereas paraganglioma arises from extra-adrenal chromaffin cells in sympathetic and parasympathetic paraganglia. Epidemiologic data on the incidence of PPGL are scarce. Older literature that dates from 1950-1979 cited a wide annual incidence range of 0. 04 to 0.95/100 000 person-years.[1] A registry study compared the age standardized incidence rates (ASRs) of PCC and sympathetic paraganglioma between 1995-1999 and 2011-2015.[2] The study noted an increase in the ASR of PCC from 0.29 in 1995-1999 to 0.46 per 100 000 person-years in 2011-2015. Similarly, the ASR of sympathetic paraganglioma increased from 0.08 in 1995-1999 to 0.11 per 100 000 person-years in 2011-2015. PPGL can be caused by a number of genetic mutations including Von Hippel-Lindau, multiple endocrine neoplasia, and succinate dehydrogenase.[3] Their tumor growth varies, and <10% of them metastasize. The triad of paroxysmal palpitations, headaches, and sweating is

Abbreviations: ASR, age standardized incidence rate; CgA, chromogranin A; CT, computed tomography; HU, Hounsfield unit; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; PCC, pheochromocytoma; PET, positron emission tomography; PPGL, pheochromocytoma and paraganglioma; ^{68}Ga, gallium-68; TSC, tuberous sclerosis complex.

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classical; however, clinical presentation can be highly variable and depends on the site of involvement and secretion of catecholamines.[4] Because of the increased use of imaging studies, many of these tumors can be found incidentally at a presymptomatic stage. Hypertension is usually present; however, up to one third of patients can be normotensive at initial presentation.[5]

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder that mainly involves the skin, kidneys, central nervous system, heart, and lungs. TSC is caused by pathogenic variants in TSC1 or TSC2, which are responsible for encoding hamartin and tuberin, respectively.[6] The interaction between these 2 proteins is critical in controlling cell growth and proliferation. TSC has been associated with NETs, mainly of parathyroid, pituitary, and pancreatic origin. A single case report showed PCC in a patient with TSC.[7] Here, we report a unique case of a patient with TSC who presented with synchronous PPGL.

Highlights

- Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors (NETs)
- NETs are uncommon in patients with tuberous sclerosis complex (TSC)
- Genomic studies have not reported hereditary or somatic variants in TSC genes in patients with PPGL

Clinical Relevance

We present an unusual case of synchronous pheochromocytoma and paraganglioma in an asymptomatic patient presenting with bilateral adrenal masses and a retroperitoneal mass. To our knowledge, this is the first case reporting the association of pheochromocytoma and paraganglioma with tuberous sclerosis complex.

Case Report

A 49-year-old woman was referred for the evaluation of bilateral adrenal and retroperitoneal masses that were noted on computed tomography (CT) performed for kidney transplant evaluation. She denied chest pain, palpitations, headaches, weight loss, abdominal pain, genitourinary symptoms, or previous hypertensive crisis. Her medical history was significant for TSC with brain, kidney, and skin involvement, hypertension (not on treatment for years), bilateral renal masses status postbilateral nephrectomies, and a previous failed kidney transplant with end-stage renal disease on dialysis. She was nonsmoker, and her family history was significant for diabetes mellitus and hypertension in the mother. Physical examination revealed a normotensive female patient with a soft abdomen, clear lungs, and macular lesions on the face and back. The laboratory test results showed normal electrolyte and liver enzyme levels with an increased serum creatinine level and mild anemia. She was noted to have increased levels of plasma normetanephrine (20.20 nmol/L; normal range, 0.00-0.89 nmol/L) and chromogranin A (CgA) (1518 ng/mL; normal range, 0-103 ng/mL). The plasma metanephrine, adrenocorticotropic hormone, serum aldosterone, renin, and free thyroxine levels were normal. The morning cortisol level was low (2 μg/dL; normal range, 6-18 μg/dL) on the low-dose dexamethasone suppression test, whereas the serum parathyroid hormone level increased in the setting of chronic kidney disease (510 pg/mL; normal range, 15-65 pg/mL). CT with the adrenal protocol showed a 3.2 × 2.9-cm retroperitoneal mass with an unenhanced attenuation value of 35.6 Hounsfield units (HU), 6.0 × 3.3-cm centrally cystic right adrenal mass (unenhanced attenuation value of 40.7 HU and absolute washout of 72%) (measured in the homogenous tumor), and 4.6 × 3.3-cm left adrenal mass (unenhanced attenuation value of 35.3 HU and absolute washout of 73%) (Fig. 1 *A*). Metaiodobenzylguanidine and gallium-68 (^{68}Ga)-DOTATATE positron emission tomography (PET)-CT scans both suggested all 3 lesions to be of neuroendocrine origin (Fig. 1 *B*). The patient was started on doxazosin 2 mg daily and, after medical optimization, underwent an extensive surgery with bilateral adrenalectomy and retroperitoneal mass excision. Pathology confirmed PCC in both adrenal glands as well as adjacent composite ganglioneuroma and paraganglioma in the retroperitoneal mass (Figs. 2 and 3). Postoperatively, she was started on systemic corticosteroids for adrenal replacement. At her 6-month follow-up, she remained normotensive without needing any antihypertensives. Her plasma normetanephrine level decreased to 0.8 nmol/L, and the CgA levels decreased to 431 ng/mL but remained elevated as expected due to end-stage renal disease.

Discussion

We present a rare case of synchronous PPGL in a patient with TSC. Our case is even more unique as the patient has composite paraganglioma/ganglioneuroma in one of the lesions. The field of PPGL has seen significant advancements with discovery of new hereditary forms and susceptibility genes. Germline or somatic mutations of the susceptibility genes can be noted in up to 60% of

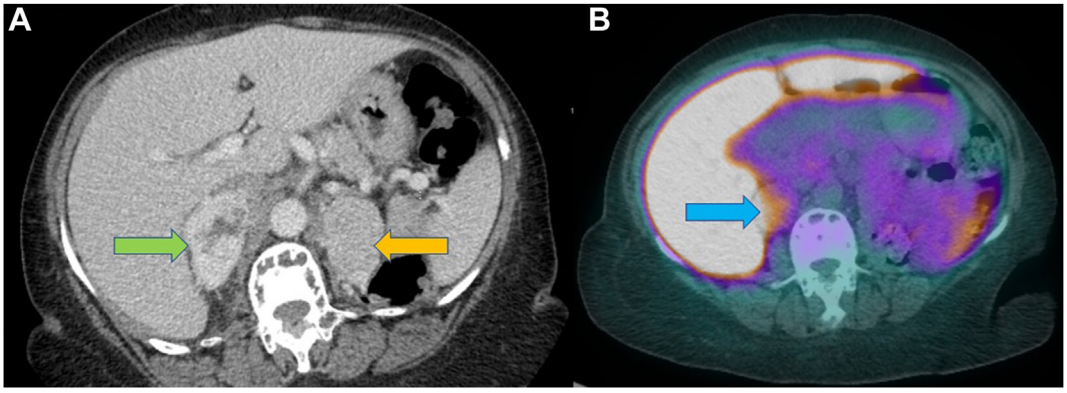

Fig. 1. *A*, Computed tomography scan showing a 6 × 3.3-cm centrally cystic right adrenal mass (green arrow) and 4.6 × 3.3-cm left adrenal mass (orange arrow arrow). *B*, Gallium-68-DOTATATE positron emission tomography/computed tomography scan showing a 3.2 × 2.9-cm retroperitoneal mass (blue arrow).

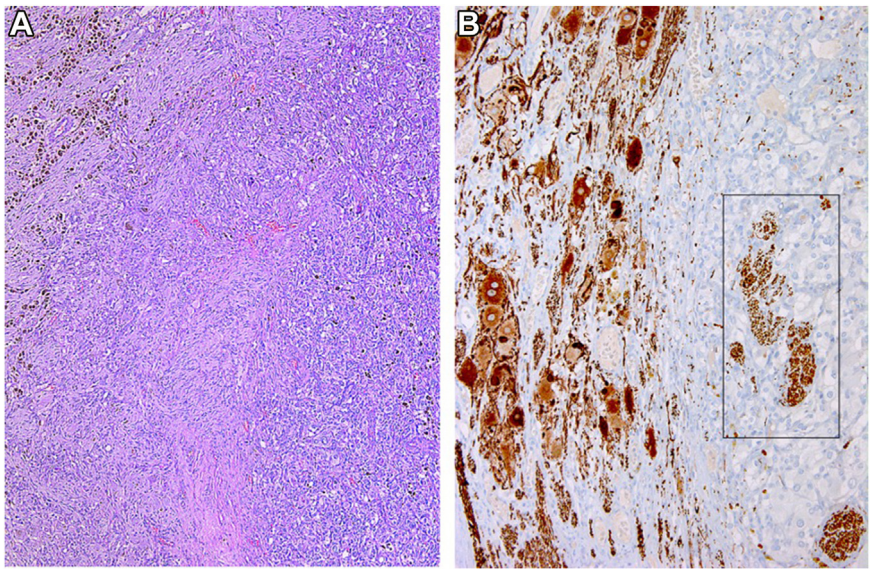

Fig. 2. *A*, Paraganglioma (right) colliding with ganglioneuroma (left) (hematoxylin and eosin staining, ×40). *B*, Left, ganglioneuroma with ganglion cells staining brown for neurofilament protein. Right, A nerve bundle within the adjacent paraganglioma in the rectangle (immunohistochemical staining, ×100).

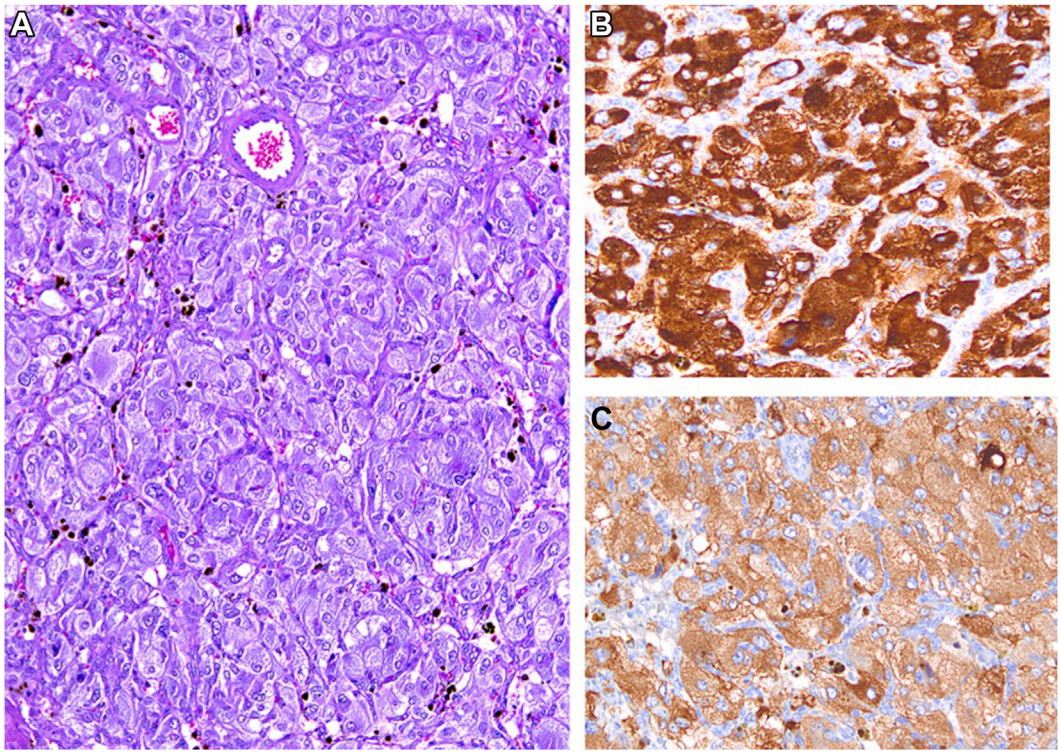

Fig. 3. *A*, The pheochromocytoma was composed of tumor cells displaying the characteristic alveolar pattern (hematoxylin and eosin staining, ×200). *B*, Tumor cells showed strong and diffuse staining for chromogranin (immunohistochemical staining, ×400). *C*, Tumor cells showed strong and diffuse staining for synaptophysin (immunohistochemical staining, ×400).

patients with PPGL.[8] Hereditary PPGL are classified into 3 clusters based on their transcription signature. Cluster 1 comprises of fumarate hydrogenase, malate dehydrogenase 2, prolyl hydroxylase 1, endothelial PAS domain-containing protein 1/hypoxia-inducible factor 2 α, and iron regulatory protein 1 genes.[9] Their biochemical profile tends to be noradrenergic. Fumarate hydrogenase–related PPGL can be multifocal and are associated with renal cell carcinomas and leiomyomatosis. Hypoxia-inducible factor 2 α–related PPGL mainly affect women and can also lead to polycythemia and somatostatinoma. Cluster 2 involves Harvey Rat sarcoma virus and chromatin remodeler alpha thalassemia X-linked intellectual disability. These tumors tend to have adrenergic biochemical profile and can present as sporadic PCC.[10] Cluster 3 involves cold-shock domain-containing E1 and fusion of upstream binding transcription factor and mastermind-like transcriptional coactivator 3. Cold-shock domain-containing E1–related tumors present with sporadic cases and can be recurrent or metastatic.[11] Alterations in any of these genes result in an increase in target genes related to the Wnt

receptor and Hedgehog signaling pathways. Mutation of upstream binding transcription factor and mastermind-like transcriptional coactivator 3 carries a poorer prognosis than other syndromic PPGL.[11] Our patient did not undergo full genetic workup. Features, such as multifocality, norepinephrine production, and ^{68}Ga-DOTATATE positivity suggest that our patient likely had cluster 1 mutation.

TSC is a rare autosomal dominant genetic disorder with variable age of onset of clinical symptoms and extent of symptoms. Its incidence is estimated to range between 1:6000 and 1:10 000 live births, and diagnosis relies on identifying pathogenic variant in TSC1 or TSC2 gene.[12] Up to 10% to 15% of patients with a clinical diagnosis of TSC can have negative conventional genetic testing; however, this does not exclude its diagnosis.[12] TSC has been reported to be associated with renal cell carcinoma, chondroma, and NETs.[7] Among the NETs, the reported tumors include pituitary adenoma, parathyroid adenoma, insulinoma, bronchial carcinoid, pancreatic gastrinoma, islet cell tumors, and PCC.[7] NETs can occur sporadically or in association with hereditary syndromes such as multiple endocrine neoplasia 1 and 2, von Hippel-Lindau syndrome, and neurofibromatosis 1. Genomic studies have not reported hereditary or somatic variants in TSC genes in patients with PPGL.[13,14] The TSC1-TSC2 complex is known to inhibit mammalian target of rapamycin (mTOR) cascade, and TSC2 inactivation can activate mTOR.[7] Its activation can lead to dysregulation of cell cycle, thereby causing tumor progression. Proto-oncogene Akt/protein kinase B is noted to be overexpressed in some NETs, and Akt has been shown activate cell activation protein mTOR and P70S6K.[15] Everolimus, which is an mTOR inhibitor, was shown to have antiproliferative effects on human PNET cells.[7] In a case of malignant islet cell tumor of pancreas in a patient with TSC, mutation analysis showed a de novo mutation (R1459X) in exon 33 of the TSC2 gene.[7] Tuberin staining was absent in tumor cells, whereas normal expression was observed in the remaining normal pancreas. In another patient with bronchial carcinoid and lymphangioleiomyomatosis, loss of heterozygosity in TSC1 was observed in the lymphangioleiomyomatosis cells, lymph nodes, uterus, and kidneys but not in the carcinoid cells.[7]

In patients with PCC, the norepinephrine and epinephrine levels can increase several times beyond the upper limit of normal; however, some patients may remain normotensive if their circulatory levels are low.[16] Sustained hypertension is mainly observed with norepinephrine, whereas postural hypotension occurs mainly with epinephrine. Patients with small tumors secreting low catecholamine levels can be normotensive, whereas PPGL that predominantly secrete dopamine can present with hypotension.[16] Plasma free metanephrines (including metanephrine and normetanephrine) have a diagnostic sensitivity of 97% to 99% and specificity of 82% to 96% for diagnosing PPGL. Urinary fractionated metanephrine has a higher sensitivity of 96% to 97% but lower specificity of 45% to 82%, whereas total metanephrine has a lower sensitivity of 60% to 88% but higher specificity of 89% to 97%.[17] CgA has a lower sensitivity (83%) but can be used to monitor for recurrence of PPGL that do not produce excess metanephrine levels.[17] Testing of PPGL can be particularly challenging in patients with chronic kidney disease because of accumulation of blood borne contaminants, unreliable urinary measurements, and up to 12-fold increase in deconjugated metanephrine in plasma.[18] Localization of the PPGL tumors can be achieved by several different procedures. CT has a sensitivity of 93% to 100% but low specificity of 70%.[19] Magnetic resonance imaging also has a high sensitivity of 93% to 100% in detecting adrenal disease and can be particularly useful in pregnant women because there is no ionizing radiation exposure.[19] PET-CT with ^{68}Ga-DOTATATE has the highest diagnostic accuracy among the diagnostic modalities. Whole-body scintigraphy with iodine-123/iodine-131-metaiodobenzylguanidine PET-CT with fludeoxyglucose-18 can be useful in patients with specific mutations or evaluating therapeutic options.[20] Surgical resection is the definitive treatment.

Disclosure

The authors have no conflicts of interest to disclose.

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