Case Report

CARNEY-STRATAKIS SYNDROME CAUSED BY A NOVEL *SDHD* MUTATION

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ABSTRACT

Objective: To raise awareness of the clinical presentation and genetic features of Carney-Stratakis syndrome (CSS) and demonstrate the importance of multimodality imaging in such patients.

Method: A case report of an unusual case of CSS due to a novel succinate dehydrogenase D (SDHD) mutation.

Results: A 39-year-old Caucasian male who presented with abdominal discomfort and reflux symptoms was found to have a gastrointestinal stromal tumor (GIST) arising from the stomach. A contrast computed tomography (CT) scan of the chest, abdomen, and pelvis subsequently revealed a right carotid body paraganglioma (PGL), a left cervical (C2) PGL, the GIST, and a left supra-adrenal tumor. He underwent a laparoscopic left supra-adrenal PGL resection. Postoperatively, he was seen in our institution, and a 68-Ga-DOTA octreotate (DOTATATE) positron emission tomography (PET) scan demonstrated avid uptake in the bilateral carotid body tumors, the GIST, and in an extracardiac PGL between the origin of the ascending aorta and main pulmonary artery that was not previously detected on the CT scan. He was diagnosed with CSS, and genetic analysis revealed a novel 3-base pair deletion starting at nucleotide position 276 (c.276_278delCTA) of the *SDHD* gene that resulted in the deletion of a single amino acid at position 93 (p.(Tyr93del)). He subsequently underwent resection of the right carotid body PGL.

Conclusion: Diagnosis of CSS and genetic evaluation should be considered in patients who present with GISTs and PGLs. A combination of conventional imaging techniques and somatostatin receptor scintigraphy is often required for the diagnosis and management of these patients. **(AACE Clinical Case Rep. 2015;1:e16-e20)**

Abbreviations:
CSS = Carney-Stratakis syndrome; **CT** = computed tomography; **DOTATATE** = 68-Ga-DOTA octreotate; **GIST** = gastrointestinal stromal tumor; **MIBG** = meta-iodobenzylguanidine; **PDGFRA** = platelet-derived growth factor receptor-α; **PET** = positron emission tomography; **PGL** = paraganglioma; **SDH** = succinate dehydrogenase

INTRODUCTION

The Carney triad was first described by Carney et al in 1977, who reported the association of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma (PGL), and pulmonary chondroma (1). The majority of these patients have 2 of these tumors, with gastric and pulmonary tumors being the most common combination. Carney-Stratakis syndrome (CSS) was first described in 2002, which is an autosomal dominantly inherited association of familial PGL and gastric sarcoma (2). The cause of this syndrome is a germline mutation in a gene encoding 1 of the succinate dehydrogenase subunits (*SDHB*, *SDHC*, or *SDHD*) (3). In contrast to CSS, the genetics of the Carney triad remains unclear. Here we report a case of CSS in a patient with a novel *SDHD* mutation who presented with gastric sarcoma and multifocal PGLs. The importance of multimodality imaging in PGLs diagnosis in these cases is also discussed.

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CASE REPORT

A 39-year-old Caucasian male with no past medical problems presented with vague abdominal discomfort and reflux symptoms in September 2012. He also described infrequent episodic fast palpitations lasting 15 to 20 minutes each and occasional sweating and headaches. No family history of pheochromocytoma or PGL syndrome was present. His father had hypertension, and there was a strong family history of lung cancer in his mother, maternal grandmother, and paternal grandfather. He had 2 children who were apparently well. He subsequently underwent upper gastrointestinal endoscopy which revealed a 44-mm high-grade epithelioid cell gastrointestinal stromal tumor (GIST) arising from the muscularis propria of the lesser curvature of stomach. This was confirmed by immunocytochemistry, which showed that the lesion stained strongly for DOG-1 (discovered on GIST-1), CD117 (c-KIT), and CD34. Further cytogenetic analysis of this lesion did not reveal mutations within the *KIT* gene (exons tested 9,11,13,17), platelet-derived growth factor receptor-α (*PDGFRA*) gene (exons tested 12,14, and 18), or *BRAF* gene (codon 600). A contrast computed tomography (CT) scan of the chest, abdomen, and pelvis revealed a 55-mm right carotid body PGL, a 8-mm left cervical (C2) PGL, the GIST protruding from the posterior wall of the stomach, and a left supra-adrenal tumor (Fig. 1). Increased uptake was noted in the left supra-adrenal PGL and revealed a left thoracic PGL on I^{123}-meta-iodobenzylguanidine (I^{123}MIBG) scanning. He underwent a laparoscopic left supra-adrenal PGL resection in February 2013 and was also treated with doxazosin (2 mg twice daily), propranolol (20 mg twice daily), and omeprazole (20 mg twice daily). He was subsequently referred to our multidisciplinary Neuroendocrine Tumour Unit for further management. Physical examination at this point revealed a medium-build male with normal heart rate and blood pressure. He was noted to have some fullness of the right neck but no other significant physical findings. The relevant results of blood tests performed are shown in Table 1. Serum chromogranin A, plasma and urinary normetadrenaline, and urinary 3-methoxytyramine were elevated. A 68-Ga-DOTA octreotate (DOTATATE) positron emission tomography (PET) scan performed at this time demonstrated avid uptake in the bilateral carotid body tumors, the GIST, and in a 25-mm extra-cardiac PGL between the origin of the ascending aorta and the main pulmonary artery (Fig. 2). The presence of GIST and multicentric PGLs (neck, thorax, and extra-adrenal) led to the suspicion of CSS, and genetic analysis was performed. Sequence analysis of the *SDHD* gene identified a 3-base pair deletion starting at nucleotide position 276 (c.276_278delCTA), resulting in the deletion of a single amino acid at position 93 (p.(Tyr93del)). This variant is novel and has not been associated with CSS in the literature. Molecular analyses of all other exons of *SDHB*, *SDHC*, *SDHD*, and the von-hippel-lindau (*VHL*) genes did not detect any sequence variants other than common polymorphisms of no known clinical significance. In addition, multiplex ligation-dependent probe amplification analysis did not reveal any evidence of a deletion or duplication within the *SDHB*, *SDHC*, *SDHD*, or *VHL* genes. He underwent resection of the right carotid body PGL in September 2013. SDHB immunochemistry for this PGL was performed using a commercially available mouse monoclonal antibody (ab14714, clone 21A11AE7; Abcam, Cambridge, UK) at a dilution of 1:800, and was found to be immunohistochemically negative (Fig. 3). He is planned to undergo GIST resection in the near future. Further therapy with Lutetium 177 (^{177}Lu) DOTA octreotate or radionuclide-targeted therapy are being considered for treatment of residual disease. In addition, genetic counseling and genetic screening is planned for the rest of his family members.

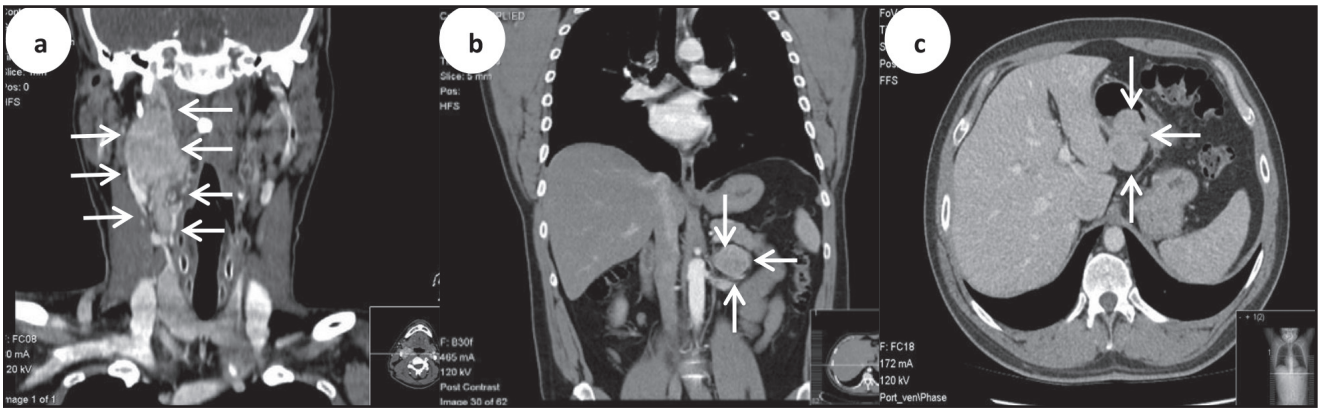

Fig. 1. The patient's contrast computed tomography images. (*A*) Saggital view of the neck showed a right carotid body PGL (*B*) Saggital view of the abdomen revealed a left supra-adrenal PGL (*C*) Coronal view of the abdomen showing the GIST, which protruded from the posterior wall of the stomach (*white arrows* = lesions). *GIST* = gastrointestinal stromal tumor, *PGL* = paraganglioma.

Table 1
Relevant Blood and Urine Test Results After Left Supra-adrenal PGL Resection

Assay	Result	Normal ranges
Chromogranin A	66 IU/L	0-27
Plasma normetadrenaline	2.20 nmol/L	<1.3nmol/L
Plasma metadrenaline	<0.10 nmol/L	<0.7nmol/L
24-hour urine metadrenaline	0.16 nmol	0-1.2
24-hour urine normetadrenaline	4.84 nmol	0-4
24-hour urine 3-methoxytyramine	11.26 nmol	0-2.5

Abbreviation: PGL = paraganglioma.

DISCUSSION

The presence of pathogenic mutations in the *SDH* subunit genes and the absence of pulmonary chondroma in the presentation clearly delineate CSS from the Carney triad. The *SDH* genes encode subunits of the heterotetrameric succinate dehydrogenase complex, a component of both the mitochondrial-respiratory chain (complex II), which catalyzes the conversion of succinate to fumarate as part of the Krebs cycle. In particular, *SDHD* (Ch11q23) encodes 1 of the 2 transmembrane subunits that anchor complex II in the inner mitochondrial membrane, and it contains a ubiquinone binding site. *SDHD* acts as a tumor suppressor gene, and mutations in *SDHD* are associated with familial PGL syndrome type 1 (PGL1). This disorder is inherited in an incompletely penetrant, autosomal dominant pattern and demonstrates maternal imprinting, so that the disease is not manifested if the mutant allele is inherited from the mother (4). *SDHD* mutations predispose patients to multiple head and neck, thoracic, and abdominal PGLs and pheochromocytomas (5), such as in our patient's case. In the original report by Passini et al, among 11 probands from 9 families with CSS, only 1 had an *SDHD* mutation caused by a deletion of a single nucleotide 57 of the *SDHD* gene (c.57delG) that resulted in a premature stop codon in the encoded mRNA (3). The mutation described in our patient results in the loss of Tyr-93 and is considered pathogenic because it has been previously recorded in a family with PGL1 (6). However, this mutation has not been described in a patient with CSS.

GISTs arise from stem cells with characteristics of interstitial cells of Cajal, the pacemaker cells in the digestive tract that regulate peristalsis. Mutations in *KIT* or *PDGFRA* have been identified as central tumor-initiating events in many sporadic GISTs (7,8). Interestingly, none of the GISTs in the patients described by Passini et al had detectable somatic mutations in either *KIT* or *PDGFRA* that are usually found in the sporadic forms. GISTs from patients with Carney triad were found to be clinically, pathologically and behaviorally different from sporadic GISTs in a study of 104 patients with this syndrome (9). The distinctive features were occurrence at a young age, female predilection, tumor multifocality, slow growth, frequent metastases (often to lymph nodes), lack of response to imatinib therapy, and unpredictable behavior. It was recently proposed that GISTs could be separated into 2

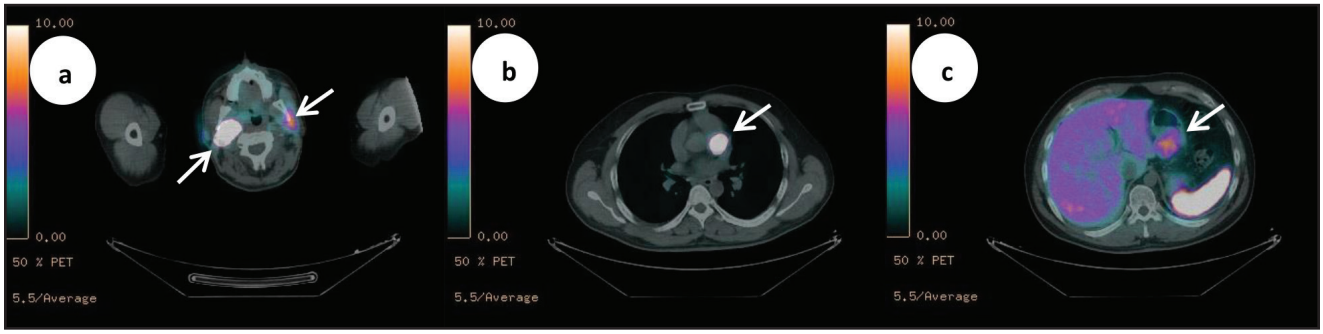

Fig. 2. The patient's 68-Ga-DOTA octreotate positron emission tomography scans. (*A*) Avid tracer uptake was noted in the bilateral carotid body PGLs (*B*) Avid tracer uptake was also observed in a 25-mm extra-cardiac PGL between the origin of the ascending aorta and the main pulmonary artery (*C*) Focal uptake of tracer along the lesser curvature of the stomach was present, which corresponds to the GIST (*white arrows* = lesions). *GIST* = gastrointestinal stromal tumor, *PGL* = paraganglioma.

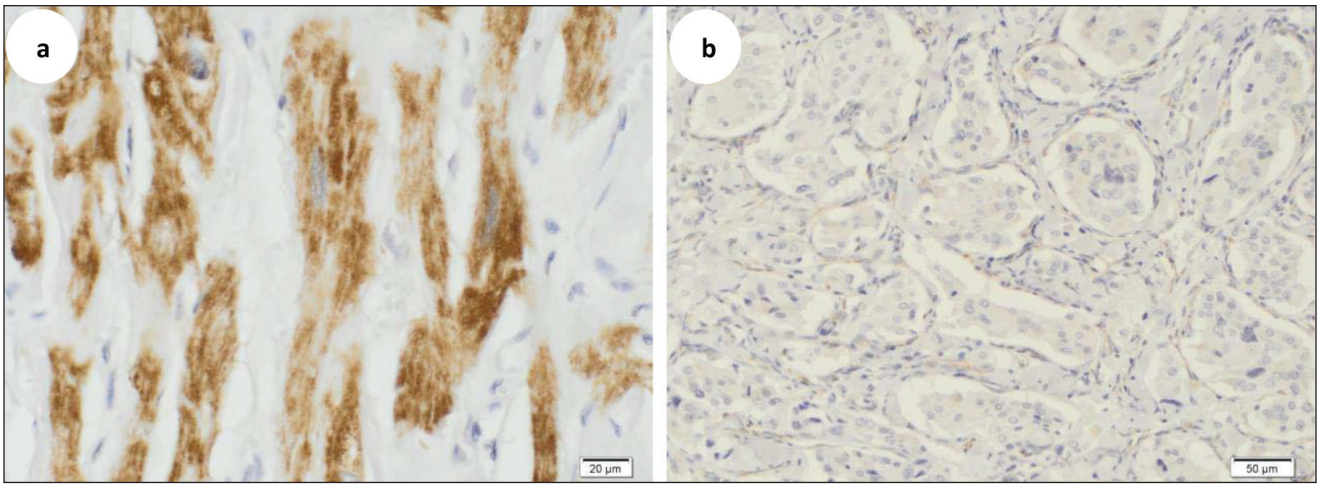

Fig. 3. SDHB immunohistochemistry. (*A*) Cardiac muscle as positive control showing positive SDHB immunostatining (*B*) Resected carotid PGL of the patient showing negative SDHB immunostaining. *PGL* = paraganglioma; *SDHB* = succinate dehydrogenase B.

groups based on immunohistochemistry for the mitochondrial protein SDHB by Gill et al (10), who provided definitive evidence that GISTs that arise in the setting of Carney triad (type 2) are characterized by negative staining for SDHB and that this staining pattern occurs rarely in unselected GISTs (type 1). Although no GISTs from subjects with CSS were available for this study, a later study on 4 GISTs from patients with CSS reported similar results (11). Hence, GISTs from patients with the Carney triad and CSS appear to be distinct from sporadic GISTs in many aspects, and some authors have suggested such tumors should be more appropriately termed gastric stromal sarcoma (9,12). An immunohistochemical absence of SDHB protein expression has also been shown to have a 100% sensitivity for the presence of *SDHB*, *SDHC*, or *SDHD* mutations in PGLs and pheochromocytomas (13). Biallelic inactivation of *SDHB*, *SDHC*, or *SDHD* genes results in complete loss of SDH activity, destabalization and proteolysis of complex II, and abnormal mitochondrial morphology (14,15). These changes likely account for the drastic decrease in SDHB expression.

It is interesting to note that the CT scan did not demonstrate the extra-cardiac PGL, and the I^{123}MIBG scan did not reveal the bilateral carotid body PGLs in our patient. In contrast, the DOTATATE PET scan showed all the lesions apart from the left supra-adrenal PGL that was resected. The diagnosis of neuroendocrine tumors such as PGLs is often done using a combination of cross-sectional imaging modalities such as magnetic resonance imaging (MRI) and CT and functional imaging, commonly with I^{123}MIBG. The latter is reported to have less sensitivity (77-90%) than CT or MRI but higher specificity (>95%) (16). However, recently published data indicate that its sensitivity is far less than previously reported for the detection of malignant pheochromocytomas (56-71%) and PGLs (18-54%) (17). The absence of norepinephrine transporter and vesicular monoamine transporters types 1 and 2 correlates with the absence of I^{123}MIBG uptake, a pattern that is associated with the presence of familial PGL disease and malignancy (18). In the series of patients described by Fottner et al, all the head and neck parasympathetic PGLs were vesicular monoamine transporter-1 negative and were not detected by I^{123}MIBG scintigraphy (18). This may explain the reason for failure to demonstrate the bilateral carotid PGLs in our patient on the I^{123}MIBG scan. The diagnostic performance of DOTATATE PET/CT in patients with PGL was recently evaluated by Maurice et al in a retrospective study including 9 patients with extra-adrenal PGL (6 head and neck, 2 abdominal, and 1 thoracic PGL) (19). DOTATATE PET/CT detected more lesions than I^{123}MIBG scintigraphy and conventional imaging, mainly in the head and neck and metastatic PGLs, confirming previous results in a smaller study from the same group. DOTATATE uptake also implies that peptide-receptor radionuclide therapy with ^{177}Lu-DOTATATE may be useful in the future therapy of this patient (20). Although the diagnostic performance of PET with various radiopharmaceuticals is clearly superior to that of MIBG in patients with extra-adrenal (particularly head and neck) and metastatic PGLs, MIBG scintigraphy continues to play a unique role in selecting patients who are suitable for ^{131}I-MIBG therapy.

CONCLUSION

The diagnosis of CSS and genetic evaluation should be considered in patients who present with GISTS and PGLs. A combination of conventional imaging techniques and newer somatostatin receptor scintigraphy is often required to correctly diagnose and manage patients with multifocal extra-adrenal PGLs, as illustrated by the present case.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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