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**Case Report**

# Three Cases of Carney-Stratakis Syndrome: A Genetically Heterogeneous Disease

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## Abstract

Carney-Stratakis syndrome (CSS) is an autosomal dominant rare syndrome, with incomplete penetrance, characterized by the association of paragangliomas and/or pheochromocytomas and gastrointestinal stromal tumors (GISTs). CSS is caused by germline heterozygous loss-of-function pathogenic variants (PVs) in the succinate dehydrogenase subunit genes (*SDHB, SDHC, SDHD*), with *SDHB* and *SDHD* being the most frequent. To date, only 2 germline *SDHC* PVs (c.43 C > T; c.405 + 1G > A) have been described in 3 patients with CSS. Three patients with CSS and very distinct clinical presentations are reported here: 1 caused by a germline *SDHC* large deletion and the others with metastatic GIST and negative genetic investigation for *SDHx* defects. Two cases (1 and 2) presented with pheochromocytoma (case 1 also with abdominal paraganglioma) and metastatic GIST. Although these 2 cases fulfilled the diagnostic criteria for CSS, the genetic investigation for *SDHx* PVs by next-generation sequencing and multiplex ligation-dependent probe amplification was negative. Case 3 had a large abdominal paraganglioma and a small low-grade GIST not associated with recurrence or metastasis. This case harbored a germline *SDHC* exon 3 deletion, not previously reported. In conclusion, CSS is a rare and morbid disease with distinct clinical presentations and genetic heterogeneity, which can contribute to underdiagnosis.

**Key Words:** Carney-Stratakis syndrome, pheochromocytoma, paraganglioma, gastrointestinal stromal tumor, succinate-dehydrogenase subunits

**Abbreviations:** CSS, Carney-Stratakis syndrome; CT, computed tomography; GIST, gastrointestinal stromal tumor; MLPA, multiplex ligation-dependent probe amplification; MRI, magnetic resonance imaging; PGL, paraganglioma; PHEO, pheochromocytoma; PV, pathogenic variant.

## Introduction

Carney-Stratakis syndrome (CSS; OMIM #606864), also reported as "paraganglioma and gastrointestinal stromal tumor syndrome" or Carney-Stratakis dyad, is an autosomal dominant rare syndrome with incomplete penetrance, characterized by the association of paragangliomas (PGLs) and/or pheochromocytomas (PHEOs) and gastrointestinal stromal tumors (GISTs) described initially in 2002 by Carney and Stratakis. It affects both males and females during childhood and adolescence [1].

CSS is caused by germline heterozygous loss-of-function pathogenic variants (PVs) in the succinate dehydrogenase subunit genes (*SDHB, SDHC, SDHD*), with *SDHB* and *SDHD* being the most frequent [2, 3]. Somatic *SDHC* PVs were previously found in GIST samples from patients without CSS diagnosis [4]. To date, only 2 germline *SDHC* PVs (c.43 C > T; c.405 + 1G > A) have been described in 3 patients with CSS [2, 5]. The Carney triad (OMIM #604287), characterized by the association of PGL, GIST, and pulmonary chondroma, is not caused by germline *SDHx* PV, but it has been associated with DNA hypermethylation in the promoter and first exon of *SDHC* [6].

Here, 3 patients with CSS and distinct clinical presentations are reported, 1 patient with a germline *SDHC* large deletion and the other 2 with metastatic GIST and negative genetic investigation for *SDHx* defects. Therefore, the spectrum of the clinical presentation and genetics of CSS was highlighted.

## Case Presentation

### Case 1

A 59-year-old woman was incidentally diagnosed with 2 different lesions (a retroperitoneal mass and a left adrenal tumor) in a routine ultrasound. She did not present with adrenergic paroxysms, headache, abdominal pain, or intestinal obstipation. The patient was previously diagnosed with severe obesity, stage 2 hypertension, and type 2 diabetes at the age of

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35 years. She had a history of cholecystectomy and partial gastrectomy because of a gastric ulcer 20 years ago. She had no family history of GIST, PHEO, or PGL. At physical examination, she presented with a body mass index = 41.2 kg/m$^2$, blood pressure = 150 × 90 mm Hg, heart rate = 90 beats/min, and no stigmas of Cushing syndrome.

### Case 2

A 62-year-old woman presented with weight loss (8 kg) and hematemesis (3 episodes in the month before hospital admission). The patient had no history of alcohol consumption. She was previously diagnosed with arterial hypertension. Her father had melanoma and her brother had prostate cancer. She had no family history of GIST, PHEO, or PGL.

### Case 3

A 42-year-old male patient was incidentally diagnosed with an expansive retroperitoneal heterogeneous lesion measuring 13.5 cm with a necrotic center. The patient underwent tumor resection in another hospital (before being referred to us). Histopathological analysis and immunohistochemistry confirmed PHEO. He mentioned no information about preoperative α-adrenergic receptor blocker. Histopathological analysis (with paraffin blocks and slides) was reviewed at our institution and confirmed the initial diagnosis of PGL.

## Diagnostic Assessment

### Case 1

Abdominal magnetic resonance imaging (MRI) scan revealed a left hypervascular para-aortic retroperitoneal mass measuring 4 cm and a solid cystic lesion with 7 cm located in the left adrenal gland topography (Fig. 1). Additionally, the MRI scan also showed a 10-cm mass, with origin in the gastric body and fundus, suggesting a mesenchymal neoplasia (GIST). Plasma metanephrine levels were < 0.2 nmol/L (38.46 pg/mL, normal range <0.5 nmol/L [96.15 pg/mL]), and normetanephrine levels were 1.5 nmol/L (288.45 pg/mL, normal range <0.9 nmol/L [173.07 pg/mL]). A meta-iodine-benzyl-guanidine labeled with iodine 131 scan demonstrated a high uptake in the left para-aortic and adrenal lesions (Fig. 1). After 2 weeks of α-adrenergic receptor blocker treatment, an upper gastric endoscopic ultrasound-guided biopsy revealed a 10-cm lesion with a hypoechoic solid component, homogenous throughout the entire lesion, originating from the muscular layer of the gastric wall. Histopathological analysis and immunohistochemistry were compatible with GIST. Pulmonary chondroma was not detected at the chest computed tomography (CT), ruling out a diagnosis of Carney triad.

### Case 2

Upper gastrointestinal endoscopy revealed a 6-cm elevated gastric fundus lesion covered by mucosa with an ulcerated region. An upper gastric endoscopic ultrasound-guided biopsy revealed a predominantly hypoechoic, irregular, heterogeneous lesion, measuring 8 cm with anechoic areas compatible with necrosis. The lesion had endophytic and exophytic projections, apparently originating from the muscular layer of the gastric fundus. Histopathology and immunohistochemistry were compatible with GIST. MRI scan detected an 8-cm gastric lesion, a 3-cm tumor in the right adrenal gland, and 3 secondary lesions in the right hepatic lobe, measuring up to 2.1 cm (Fig. 2). Biochemical investigation revealed a plasma normetanephrine level of 5.2 nmol/L (999.96 pg/mL, normal range <0.9 nmol/L [173.07 pg/mL]) and metanephrine levels of 0.5 nmol/L (96.15 pg/mL, normal range <0.5 nmol/L [96.15 pg/mL]), confirming the biochemical diagnosis of pheochromocytoma. Pulmonary chondroma was not detected on the chest CT.

### Case 3

During the patient follow-up, a positron emission tomography CT imaging with 2-[(18)F]fluoro-2-deoxy-D-glucose revealed an undetermined nodular lesion in the posterior gastric body wall, suggestive of a neoplastic process (Fig. 3). A subsequent upper gastrointestinal endoscopy indicated a gastric elevated subepithelial lesion, and the histopathology with immunohistochemistry was compatible with GIST. An abdominal CT scan showed a 1.9-cm lesion in the gastric body. Chest CT did not indicate pulmonary chondroma.

## Treatment

### Case 1

The patient started perioperative preparation with α-adrenergic receptor blocker (doxazosin 2 mg twice per day) and a high-sodium diet (3-5 g/d). After a week of α-adrenergic blocker, a ß-adrenergic receptor blocker was initiated to control reflex tachycardia. Blood pressure remained well controlled (120 × 80 mm Hg) without postural hypotension. She successfully underwent a subtotal gastrectomy, left adrenalectomy, and resection of the para-aortic lesion. Six peritoneal lymph nodes were also resected. Histopathological analysis revealed PHEO (Pheochromocytoma of the Adrenal gland Scaled Score [PASS] score = 4, Ki67% < 1%, chromogranin positive, synaptophysin positive) and PGL (Ki67% 1%-2%, chromogranin positive, synaptophysin positive). A metastatic abdominal lymph node was detected with positive staining for chromogranin and synaptophysin. Histopathological analysis of the gastric lesion evidenced an epithelioid GIST (mitotic count: >3/5 mm$^2$) positive for C-KIT (CD117), CD34, and DOG1. Therefore, the diagnosis of CSS was confirmed.

### Case 2

The patient started perioperative preparation with α-adrenergic receptor blocker (doxazosin 2 mg twice per day) and a high-sodium diet (3-5 g/d). After a week of α-adrenergic blocker, a ß-adrenergic receptor blocker was initiated to control reflex tachycardia. Blood pressure remained well controlled (110 × 70 mm Hg) without postural hypotension. The patient underwent a right laparoscopic adrenalectomy. After a month of adrenalectomy, the patient underwent GIST resection. Histopathological analysis confirmed PHEO (PASS = 0, Ki67% < 1%, chromogranin positive, synaptophysin positive) and metastatic GIST (spindle cell 80% and epithelioid 20%; mitotic count: 11/5 mm$^2$) positive for C-KIT (CD117), CD34, and DOG1. The association between PHEO and GIST fulfilled the diagnostic criteria for CSS.

### Case 3

This patient underwent a segmental gastrectomy, which removed the lesion in the posterior wall of the stomach. Histopathological analysis confirmed PGL (Ki67% < 1%, chromogranin positive, synaptophysin positive) and

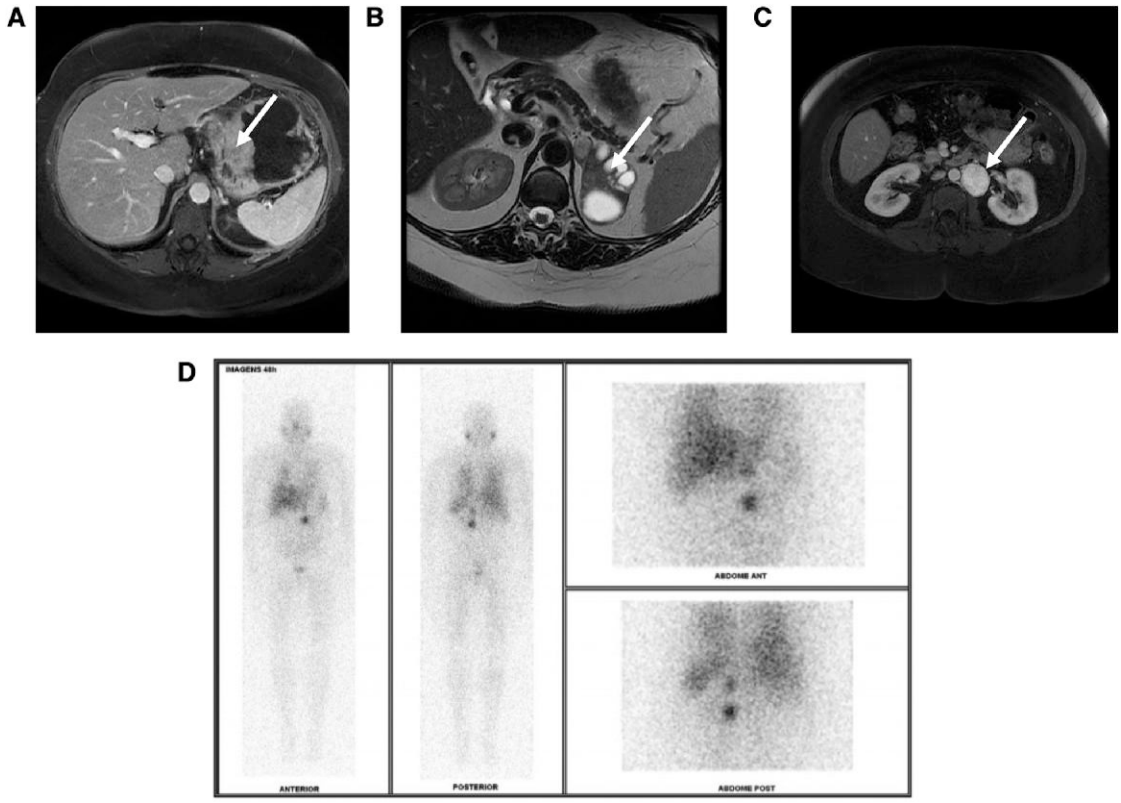


**Figure 1.** (A) Magnetic resonance imaging (MRI) scan showing a 10-cm GIST with apparent origin in the gastric body and fundus (white arrow). (B) Axial $T_2$-weighted MRI showing a 7-cm left solid cystic pheochromocytoma (white arrow). (C) Axial $T_2$-weighted MRI indicating 4-cm para-aortic paraganglioma (white arrow). (D) Meta-iodine-benzyl-guanidine labeled with iodine 131 ($^{131}$I-MIBG) scan demonstrating a high uptake in the left para-aortic and adrenal lesions. GIST, gastrointestinal stromal tumor.

epithelioid GIST (mitotic count: 3/5 mm$^2$) positive for C-KIT (CD117), CD34, and DOG1.

## Outcome and Follow-up

### Case 1

After surgical treatment, the patient's plasma normetanephrine normalized and MIBG uptake turned negative. After 2 years of follow-up, no recurrence of paraganglioma and pheochromocytoma was detected, but she exhibited progression of peritoneal lymph node metastases from GIST. Genetic analysis of *SDHB, SDHD, SDHC, SDHA,* and *SDHAF2* genes in DNA from peripheral blood lymphocytes using next-generation sequencing and multiplex ligation-dependent probe amplification (MLPA) was negative. GIST did not harbor somatic *c-KIT* and *PDGFRA* PVs. Immunohistochemistry for SDHB was positive in the pheochromocytoma, paraganglioma, and GIST (Fig. 4A).

### Case 2

After adrenalectomy, the patient's plasma normetanephrine and metanephrine levels normalized. Imatinib treatment was initiated for GIST liver metastasis. Genetic analysis of *SDHB, SDHD, SDHC, SDHA,* and *SDHAF2* genes in DNA from peripheral blood lymphocytes using next-generation sequencing and MLPA was negative. Somatic *c-KIT* and *PDGFRA* PVs were not detected in the GIST tumor sample. PHEO and GIST showed a positive staining for SDHB (Fig. 4B).

### Case 3

The patient's plasma normetanephrine and metanephrine levels remained normal during the follow-up. He did not present with GIST recurrence after 18 months of follow-up. Genetic investigation of CSS in DNA from peripheral blood lymphocytes revealed a germline *SDHC* exon 3 deletion detected using MLPA and next-generation sequencing (Fig. 3). Somatic *c-KIT* and *PDGFRA* PVs were not detected in the GIST tumor sample. Immunohistochemistry for SDHB was positive in the paraganglioma. GIST showed negative staining for SDHB (Fig. 4C).

## Discussion

CSS is a rare syndrome characterized by 2 types of tumors, PHEO/PGL and GIST. In contrast to the Carney triad, which has not been so far associated with germline defects, CSS is mainly caused by germline PVs in *SDHB* and *SDHD* [2]. *SDHC* loss-of-function PVs were rarely reported in CSS [2]. To date, only 2 germline *SDHC* PVs (c.43 C > T; c.405 + 1G > A) have been described in 3 patients with CSS [2, 5]. Therefore, a germline *SDHC* exon 3 deletion was first reported here as a cause of CSS in a patient with GIST and abdominal PGL (case 3). Case 3 had a small, low-grade GIST not associated with recurrence or metastasis.

The other 2 cases presented with PHEO (case 1 also with PGL) and metastatic GIST. Although these 2 cases fulfilled the diagnostic criteria for CSS, the genetic investigation for *SDHx* genetic defects by next-generation sequencing and MLPA was negative.

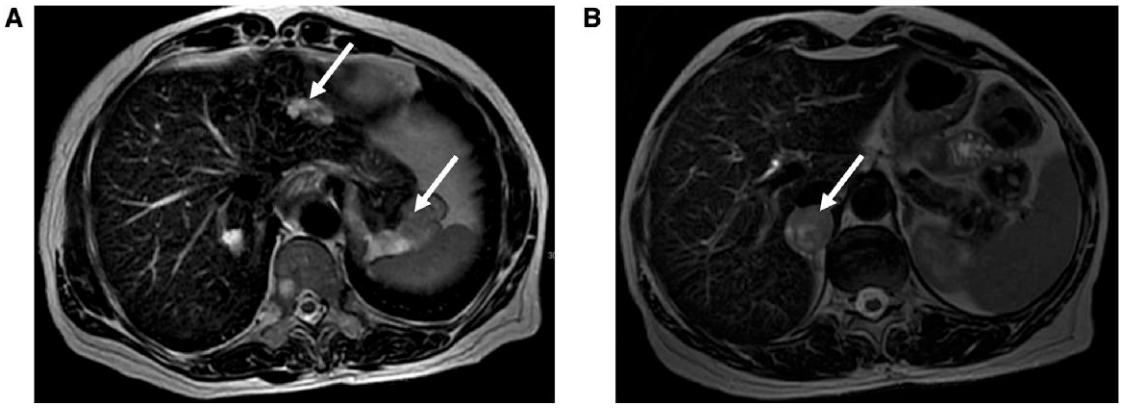


**Figure 2.** (A) Axial $T_2$-weighted magnetic resonance imaging (MRI) scan indicating an 8-cm GIST and a metastatic GIST liver lesion (white arrows). (B) Axial $T_2$-weighted magnetic MRI scan showing a 3-cm right pheochromocytoma (white arrow). GIST, gastrointestinal stromal tumor.

SDHB immunohistochemistry is a reliable tool to identify patients with genetic defects in the *SDHB*, *SDHD*, or *SDHC* genes, although 10% of the *SDH*-deficient tumors can present SDHB immunoreactivity [7]. In our study, immunohistochemistry for SDHB was positive in the PHEO and PGL of the 3 cases. GIST from cases 1 and 2 (not harboring germline *SDHx* genetic defects) presented a positive immunoreactivity for SDHB. Only the GIST from case 3 (harboring a germline *SDHC* exon 3 deletion) was negative for SDHB staining, suggesting a second somatic event in the *SDHC* gene (such as promoter hypermethylation). All 3 cases have not exhibited pulmonary chondromas so far. Boikos et al reported *SDHC* promoter hypermethylation (*SDH*-epimutant) in 6 of 11 GIST from patients with Carney triad [8]. Interestingly, *SDH*-epimutant GIST was also identified in a patient with CSS [8]. Non-*SDH*-deficient GISTs are caused by germline *KIT/PDGFRA* and are rarely associated with lymph

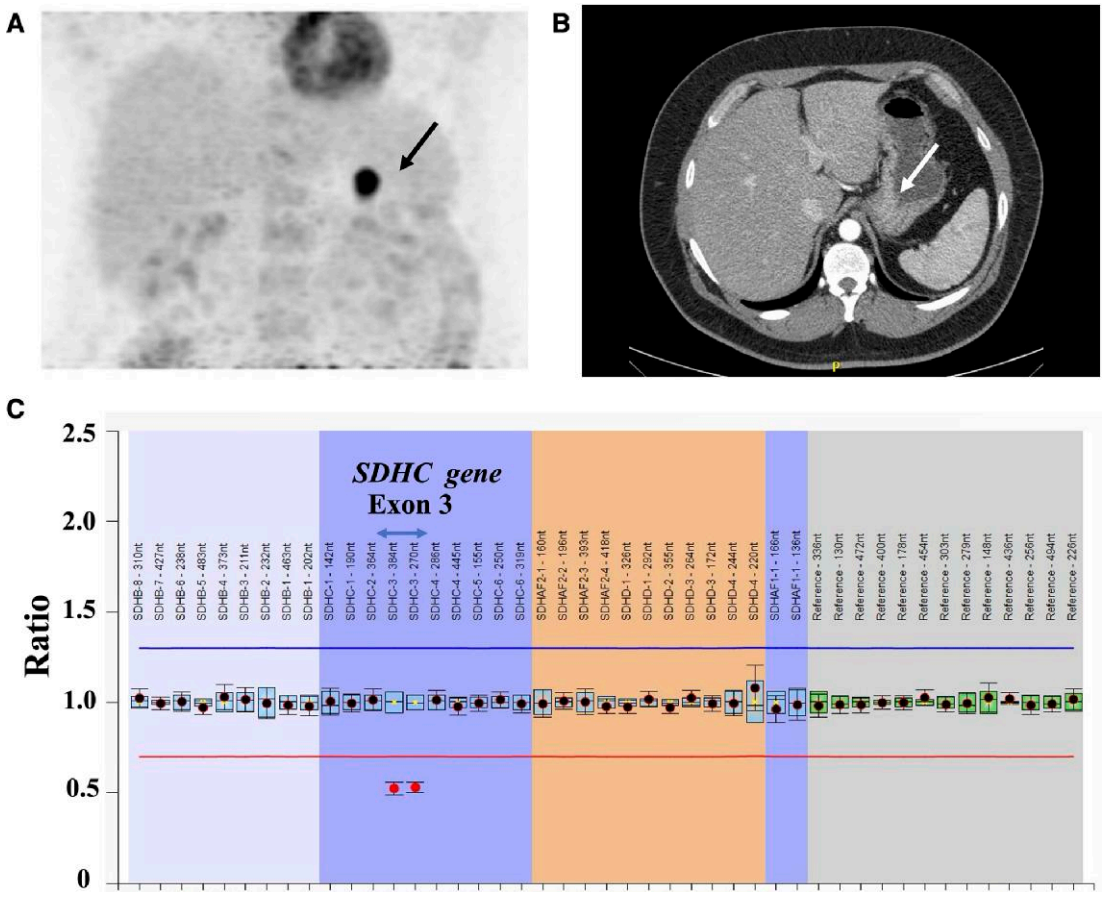


**Figure 3.** (A) Positron emission tomography (PET)-CT imaging with 2-[(18)F]fluoro-2-deoxy-D-glucose (FDG) revealing an undetermined nodular lesion in the posterior gastric body wall, suggestive of a neoplastic process (black arrow). (B) CT scan revealed a lesion in the gastric body, measuring 1.9 cm (white arrow). (C) Genetic investigation revealed a germline *SDHC* exon 3 deletion detected using multiplex ligation-dependent probe amplification (MLPA). CT, computed tomography; GIST, gastrointestinal stromal tumor.

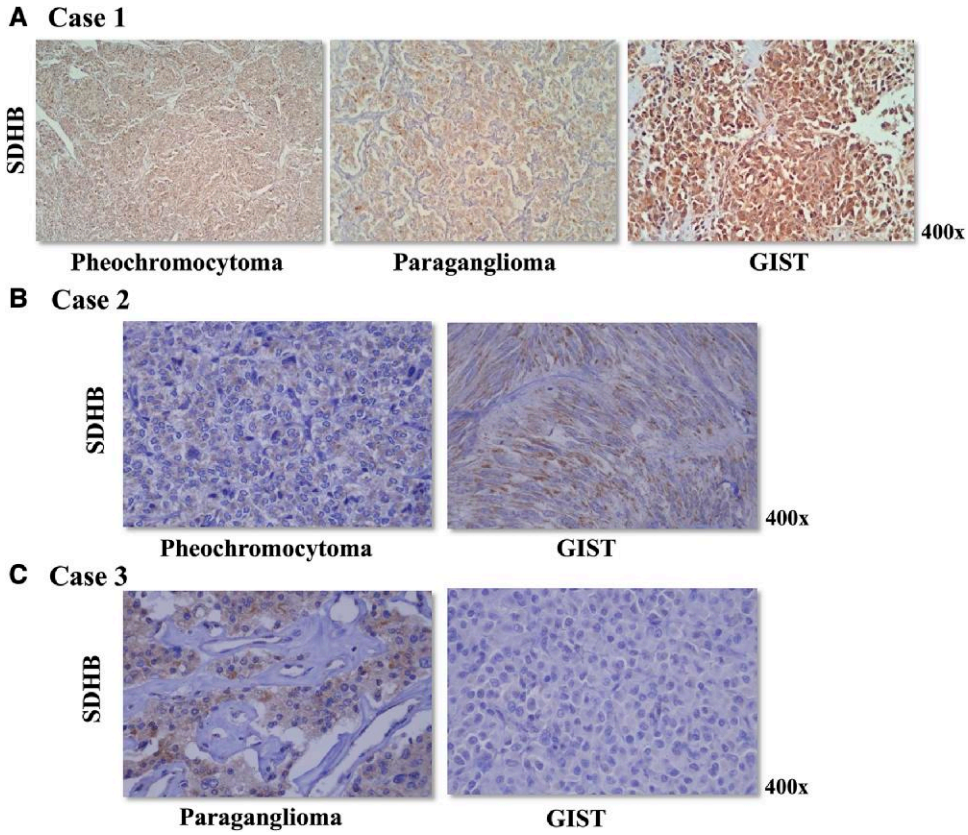


**Figure 4.** (A) Immunohistochemistry for SDHB was positive in the pheochromocytoma, paraganglioma, and GIST of case 1. Genetic investigation for *SDHx* pathogenic variants and large deletions was negative in the germline DNA and all 3 tumors samples from case 1. (B) Pheochromocytoma and GIST of case 2 displayed a positive staining for SDHB. Case 2 did not harbor germline pathogenic variants or large deletions in the *SDHx* genes. (C) Case 3 harbored a germline *SDHC* exon 3 deletion. Immunohistochemistry for SDHB was positive in the paraganglioma. GIST displayed a negative staining for SDHB, suggesting a second somatic event in the *SDHC* (such as promoter hypermethylation).

node metastasis [1]. However, 2 very aggressive metastatic non-*SDH*-deficient GIST associated with CSS are described here. Our cases support the concept that CSS is a genetically heterogeneous disease, not only caused by germline *SDHx* defects.

Very rare patients with CSS but without *SDHB*, *SDHD*, or *SDHC* PVs have been reported [2, 9]. However, these cases were not properly investigated using next-generation sequencing and/or MLPA to exclude large deletions, as shown by 1 of our cases. Therefore, the first 2 fully investigated cases of CSS without a defined genetic etiology are presented here. Although *SDHx* defects have not been identified in the Carney triad, *SDHC*-specific hypermethylation is considered the molecular signature of GIST associated with the Carney triad and wild-type-GIST [6, 10].

In addition to genetic heterogeneity, 3 cases of CSS with very distinct clinical presentation were reported. Case 1 had PHEO, PGL, and metastatic GIST, whereas case 2 had a predominance of GIST-related symptoms and a clinically silent PHEO (despite the fact normetanephrine levels were highly elevated). Interestingly, both cases had metastatic GIST. Different from these 2 cases, case 3 had an incidental diagnosis of a large abdominal PGL (data not available about function) and a subsequent diagnosis of a small low-grade GIST during follow-up. Case 3 harbored a germline *SDHC* exon 3 deletion, as previously mentioned.

In conclusion, CSS is a rare and morbid disease with distinct clinical presentations and genetic heterogeneity, which can contribute to underdiagnosis. In this manuscript, a large germline *SDHC* deletion was first described as a cause of CSS, and 2 cases of CSS with metastatic GIST not associated with germline *SDHx* genetic defects were reported.

## Learning Points

- Carney-Stratakis syndrome (CSS), characterized by the association of pheochromocytoma/paraganglioma and gastrointestinal stromal tumor), is a rare and morbid condition, but its recognition and diagnosis are associated with greater clinical benefits for the patients.
- The distinct patterns of clinical presentation in CSS patients might contribute to underdiagnosis of this disease.
- CSS is mostly caused by germline genetic defects in *SDHB*, *SDHD*, and *SDHC* genes.
- CSS seems to be a genetic heterogeneous disease not only caused by germline *SDHx* pathogenic variants. Other genetic etiologies remain to be defined.

## Contributors

All authors made individual contributions to authorship. ECL and GFCF: was involved in the review of medical records, preparation of images and manuscript writing. FF-C and LSS: were involved in the genetic investigation and preparation of images; ICS: was involved in the anatomopathological analysis and immunohistochemistry; MQA: was involved in the diagnosis and management of the patients,

conception and critical review of the manuscript. All authors reviewed and approved the final draft.

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## Disclosures

MQA is a board member of JCEM Case Reports. The other authors have nothing to disclose.

## Informed Patient Consent for Publication

Signed informed consent obtained directly from the patients.

## Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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