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Case Report

Carney-Stratakis syndrome: A dyad of familial paraganglioma and gastrointestinal stromal tumor ☆,☆☆

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ABSTRACT

Carney-Stratakis syndrome is a rare, distinct dyad of familial paraganglioma and gastrointestinal stromal tumor, and is associated with germline mutations in the succinate dehydrogenase genes SDHB, SDHC, and SDHD. We present a unique case of a 45-year-old woman with Carney-Stratakis syndrome who initially presented with a palpable left neck mass. Further workup demonstrated 2 paragangliomas in the neck and multiple SDHB deficient gastrointestinal stromal tumors of the stomach. We describe the imaging findings and clinical course of this rare syndrome.

Introduction

Carney-Stratakis syndrome, first described in 2002, describes the dyad of familial paraganglioma and gastrointestinal stromal tumor [1]. It is a unique entity, separate from the previously described Carney triad, which noted the association between paraganglioma, gastrointestinal stromal tumor (GIST), and pulmonary chondroma. Carney-Stratakis syndrome is associated with germline mutations in the succinate dehydrogenase genes SDHB, SDHC, and SDHD, with autosomal dominant inheritance and incomplete penetrance [2–4]. We describe a case of Carney-Stratakis syndrome in a 45-year-old female patient who initially presented with a palpable neck mass.

Case report

A 45-year-old woman with no significant past medical or surgical history presented following several months of a palpable left neck mass. Besides being palpable, the lesion was otherwise asymptomatic. The patient underwent ultrasound-guided biopsy at an outside institution, pathology demonstrating neuroendocrine tumor, with immunostains positive for synaptophysin, chromogranin and CD56, consistent with paraganglioma. Contrast-enhanced computed tomography (CT) of the neck, as well as contrast-enhanced CT of the chest, abdomen and pelvis were ordered for further evaluation.

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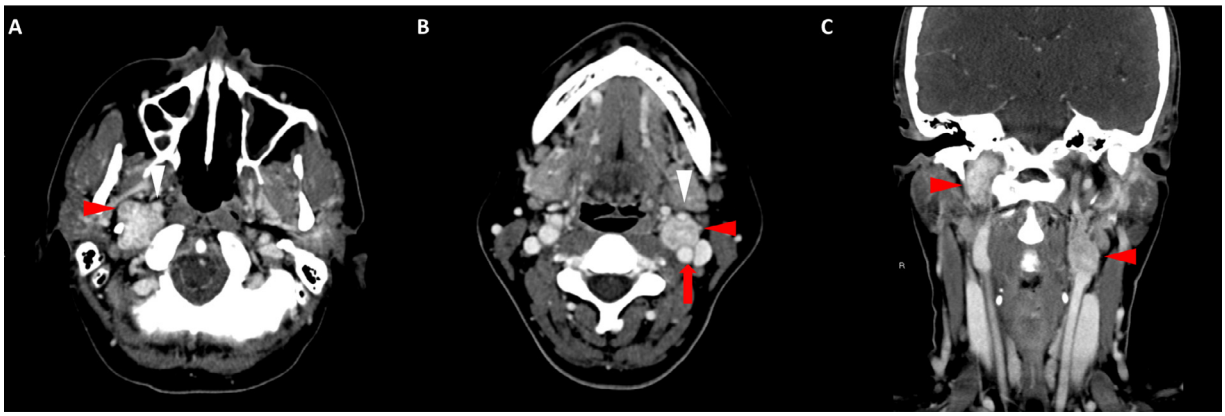

Fig. 1 – Right vagal and left carotid body paragangliomas. (A) Axial contrast-enhanced CT in the axial plane demonstrates an avidly enhancing mass (red arrowhead) in the right carotid space, posterior to the right internal carotid artery (white arrowhead) and medial to the styloid process. (B) Axial contrast-enhanced CT demonstrates an avidly enhancing mass (red arrowhead) in the left carotid space, which splays the internal carotid artery posteriorly (red arrow), and the external carotid artery anteriorly (red arrow). (C) Coronal contrast-enhanced CT shows both enhancing masses (red arrowheads). (Color version of figure is available online.)

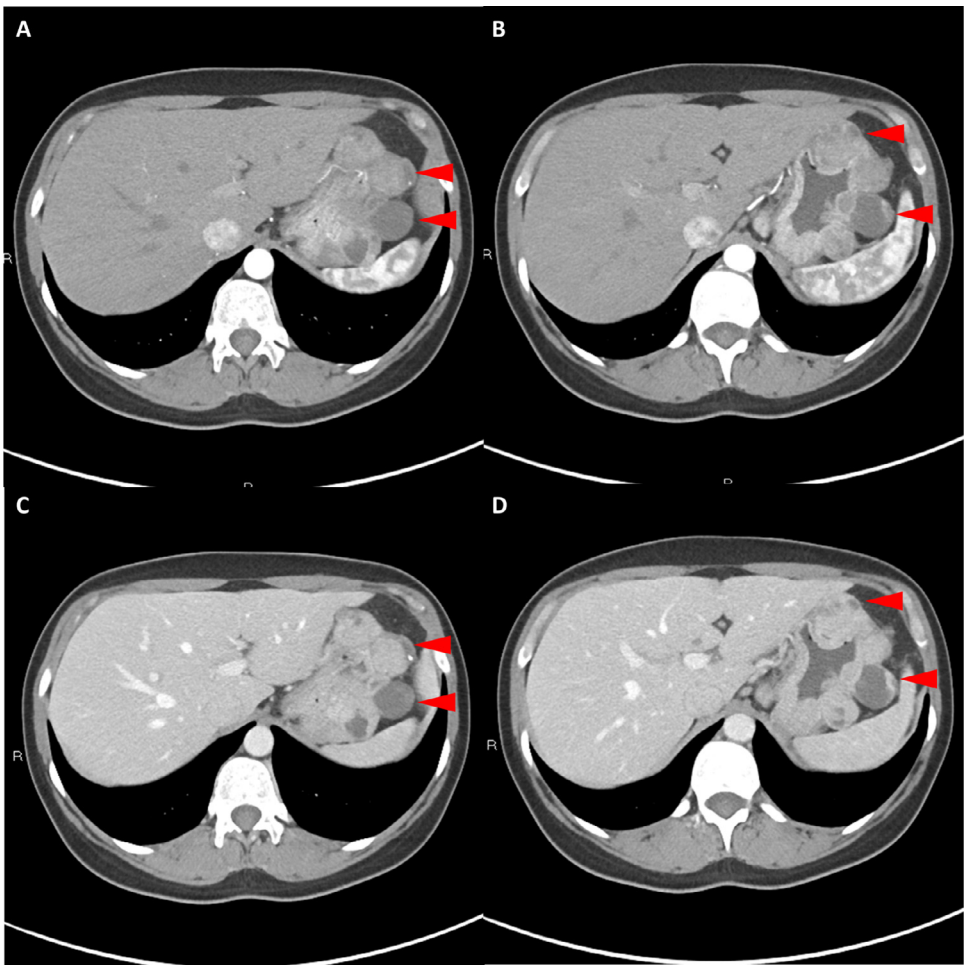

Fig. 2 – Axial CT images of multiple gastrointestinal stromal tumors. (A and B) Axial arterial phase contrast-enhanced CT images and (C and D) Axial venous phase contrast-enhanced CT images demonstrate multiple rounded, heterogenous, enhancing masses with solid and cystic components. The masses are submucosal in location and exophytic in configuration.

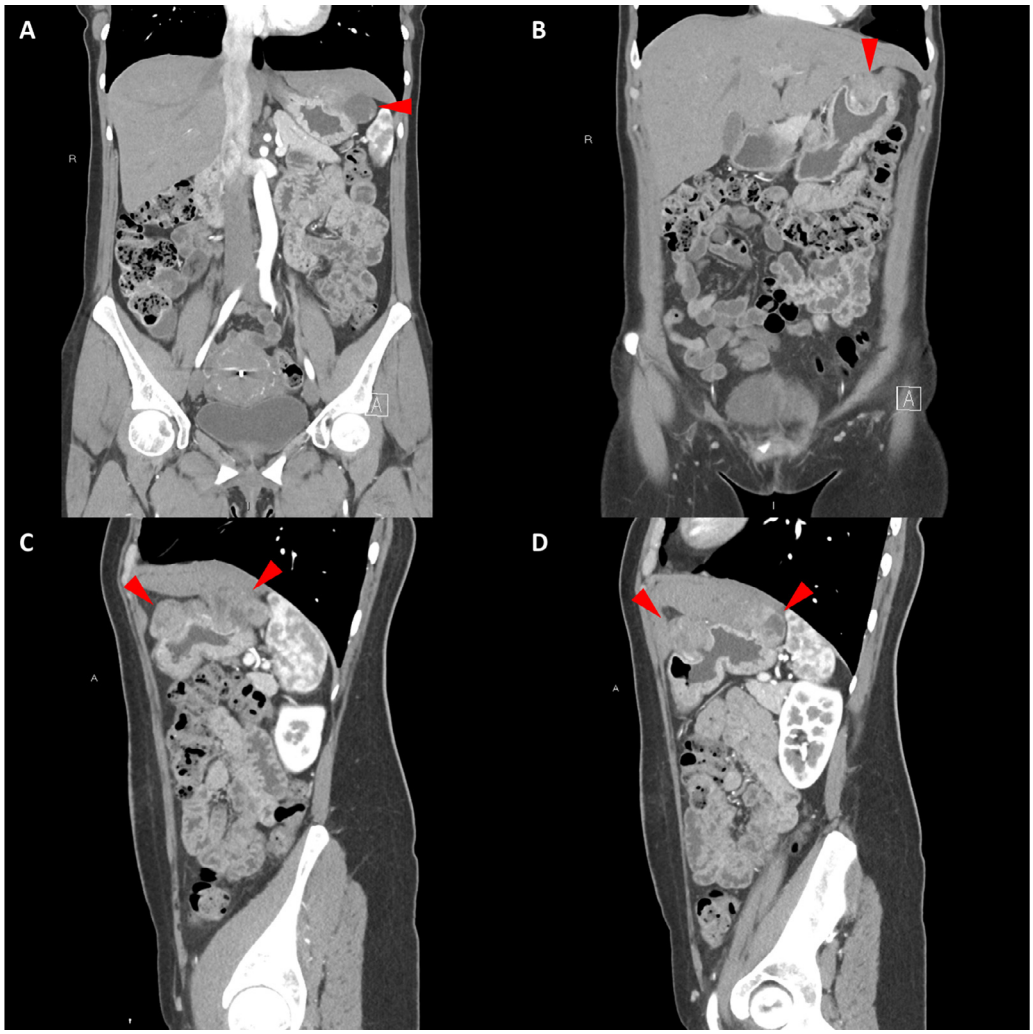

Fig. 3 – Coronal and sagittal images of multiple gastrointestinal stromal tumors. (A and B) Coronal arterial phase contrast-enhanced CT images show the exophytic masses arising from the gastric cardia. (C and D) Sagittal arterial phase contrast-enhanced images demonstrate the masses' heterogeneity and exophytic configuration.

Contrast-enhanced CT of the neck demonstrated 2 avidly enhancing masses. One was in the right side of the neck in the carotid space posterior to the right internal carotid artery and medial to the styloid process, measuring 24 × 24 × 30 mm, with lateral displacement of the jugular vein (Fig. 1A). A second was located in the left carotid space splaying the external and internal carotid arteries just above the bifurcation measuring 15 × 18 × 22 mm (Fig. 1B). Imaging findings were consistent with a right vagal and a left carotid body paraganglioma, compatible with the prior biopsy results.

Contrast-enhanced arterial and venous phase CT of the chest, abdomen, and pelvis demonstrated multiple rounded, mostly hypervascular, heterogeneous masses, with both cystic and solid components, arising from the gastric fundus and body (Figs. 2–4). The lesions were partially exophytic in configuration, and thought to be submucosal in location. In the setting of multiple synchronous paragangliomas in the neck, the initial differential diagnoses included multiple paragangliomas, multiple GISTs, as well as metastatic disease.

The patient underwent serum metanephrine testing, which was normal, followed by endoscopic ultrasound and biopsy of the gastric submucosal lesions, the largest having central ulceration. Pathology demonstrated gastrointestinal stromal tumor, positive for CD117/KIT immunolabeling. Given ulceration, surgical resection was planned. Although initial plans were sleeve gastrectomy, lymphadenopathy was seen along the lesser curvature, and the procedure was converted to an open total gastrectomy with Roux-en-Y reconstruction and celiac lymphadenectomy. Pathology demonstrated multiple gastric tumors, of mixed GIST subtype, and demonstrating loss of SDHB. Three of 16 regional lymph nodes demonstrated metastatic GIST.

Approximately 4 months later, the patient underwent left carotid body tumor resection, requiring intraoperative management of carotid artery bleeding. Pathology was consistent with paraganglioma. Interestingly, SDHB staining was retained.

The patient was not placed on any adjuvant treatment, as the patient's GISTs lacked mutations in KIT or platelet-derived

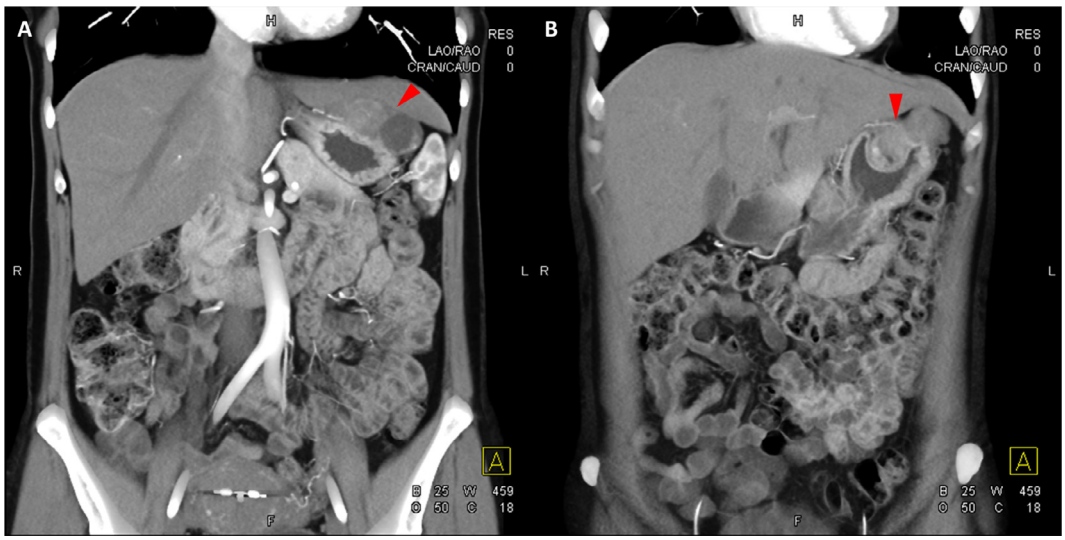

Fig. 4 – Three dimensional representations of the gastrointestinal stromal tumors. (A and B) 3D visualization of the gastrointestinal stromal tumors in the arterial phase and in the coronal plane provides further anatomic detail and spatial information.

growth factor alpha (PDGFRA). The patient has been undergoing close imaging follow-up with magnetic resonance imaging, without recurrent GIST or paragangliomas, and has only had minor enlargement of the right paraganglioma over a 3-year period.

Discussion

We present this unique case of a de novo diagnosis of Carney-Stratakis syndrome in an otherwise healthy and asymptomatic 45-year-old woman. Carney-Stratakis syndrome, the dyad of paraganglioma and GIST, has autosomal dominant inheritance and incomplete penetrance [1–4]. The mean age of diagnosis was 23 years in the initial cohort of patients and was seen in both male and female patients [1,3–5]. Although Carney-Stratakis syndrome has overlap with the Carney Triad (the association of GIST, paraganglioma, and pulmonary chondroma), the Carney Triad is sporadic, has female predominance, and is not associated with mutations in KIT, PDGFRA, or SDH genes [1,4,5].

Carney-Stratakis syndrome is one of the familial GIST syndromes, which also includes primary familial GIST syndrome and neurofibromatosis type 1. However, while the familial GIST syndrome is associated with KIT and PDGFRA mutations, Carney-Stratakis syndrome is associated with germline mutations of the succinate dehydrogenase subunits B, C, and D [2,3,5].

SDH-deficient GISTs, as seen in Carney-Stratakis syndrome are rare, and are thought to comprise only 7.5% of all GISTs [6,7]. However they have unique characteristics that can help distinguish them from the more common KIT and PDGFRA mutated GISTs. They are more frequently associated with female gender, and present at a younger age [6–8]. Pathologically, the tumors are most commonly located in the stomach, are multifocal, and demonstrate epithelial hypercellular histology [7,8]. A study of multi-detector CT findings in a cohort of 34 patients with SDH-deficient GISTs found metastases in 82% of these patients [7,8]. Liver was the most common site of metastasis (71%), followed by peritoneum (59%), nodes (53%) and lung (29%) [7]. While lymph node metastases are frequently seen in SDH-deficient GISTs, they are otherwise uncommon in GISTs [7,8]. However, even in the setting of metastatic disease, SDH-deficient GISTs had an overall indolent clinical course, though patients may develop late onset metastases, requiring long term follow-up [6–8].

SDH gene mutations, as seen in Carney-Stratakis syndrome, are also seen in familial paraganglioma syndromes type 1-5. Other familial pheochromocytoma and paraganglioma syndromes include Von-Hippel Lindau, multiple endocrine neoplasia type 2, and neurofibromatosis type 1 [9]. Notably, compared to sporadic paragangliomas, paragangliomas with SDHB mutations have a higher risk for metastatic disease, and are also associated with renal cell carcinoma and papillary thyroid carcinoma, in addition to GISTs [9–11].

Management of SDH-deficient GISTs and paragangliomas can also vary. While surgery is considered a first line treatment in GISTs, given the higher risk of lymphovascular invasion in SDH-mutated GISTs, there is also a role for lymph node sampling [12]. Additionally, the tyrosine kinase inhibitors typically used for GISTs, such as imatinib, have demonstrated less efficacy for SDH-deficient tumors given the absence of the target mutation [12]. Surgery is also the favored treatment for localized and symptomatic paragangliomas, and may require a multidisciplinary approach [13]. However, ongoing research is being done to identify viable treatments for SDH-deficient tumors owing to their unique biochemistry [9,12].

In conclusion, this case demonstrates the imaging findings of multiple paragangliomas and gastric GISTs associated with Carney-Stratakis syndrome. Although a rare diagno-

sis, it is important to consider syndromic associations in the setting of multiple paragangliomas or GISTs, as an accurate diagnosis can have significant implications in treatment and follow up.

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