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Case Report

Carney-Stratakis Syndrome presenting as occult mediastinal paraganglioma ☆

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ABSTRACT

Carney-Stratakis Syndrome is defined as the combination of a paraganglioma and a gastrointestinal stromal tumor. This is recognized as unique from the more commonly known Carney Triad, which in addition to the above also has a pulmonary chondroma present. We present a case of Carney-Stratakis Syndrome which highlights the value of multimodality imaging in arriving at the diagnosis, as well as the role of genetic testing for definitively differentiating it from the more commonly recognized Carney Triad.

Introduction

First described in 1977, the Carney Triad refers to a rare syndrome that clinically manifests as synchronous or metachronous gastrointestinal stromal tumor (GIST), pulmonary chondroma (PC), and extra-adrenal paraganglioma (PGL) [1]. However, another distinct and equally rare entity referred to as Carney-Stratakis Syndrome (CSS) has been subsequently characterized, which manifests as PGL and GIST alone [2]. Differentiating between the 2 syndromes is difficult, but has significant implications for the patient and family members; as Carney Triad is the result of sporadic postzygotic mutations, whereas CSS can be associated with a germline mutation and passed to children. Here, we present a case of CSS and discuss the pathophysiology of the syndrome.

Case report

A 38-year-old woman presented to the emergency department with worsening, nonspecific abdominal pain. As a teenager, she was diagnosed with GIST of the stomach for which she underwent resection with Roux-en-Y reconstruction. Given her oncologic history and symptoms, a 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan was obtained; this demonstrated recurrent GIST in the small bowel along with hepatic metastatic disease (Fig. 1). A hypermetabolic focus in the mediastinum was identified as concerning for metastatic adenopathy but no definite CT correlate was found on a concurrent diagnostic chest CT.

The patient underwent surgical resection of the recurrent small bowel tumor and hepatic metastasis with

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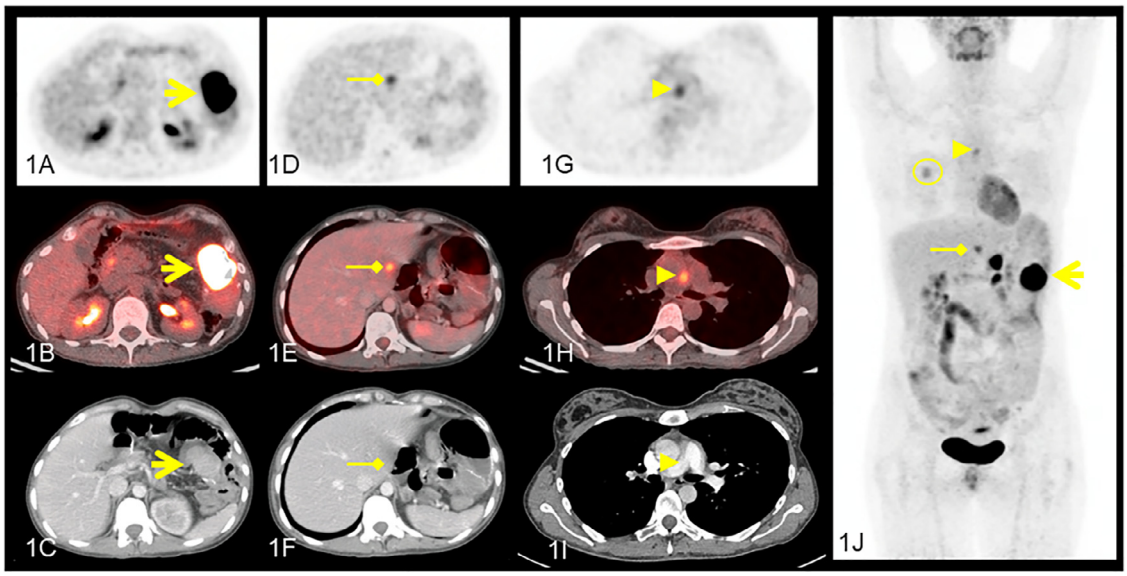

Fig. 1 – Selected images from the initial FDG PET/CT and concurrent contrast-enhanced CT examinations in this patient status post Roux-en Y gastric bypass. Transaxial FDG PET (A) fused FDG PET/CT (B) and contrast-enhanced CT (C) images show a hypermetabolic intraluminal GIST within the small bowl (yellow arrowhead). Transaxial FDG PET (D) fused FDG PET/CT (E) and contrast-enhanced CT (F) images through the liver show a hypermetabolic GIST metastasis to segment IV of the liver (diamond arrow). Transaxial FDG PET (G) fused FDG PET/CT (H) and contrast-enhanced CT (I) images show a focus of mildly increased FDG uptake in the mediastinum (triangles), without a CT correlate. Coronal FDG PET maximum intensity projection (MIP; J) demonstrates corresponding foci, with one additional focus localized to the right breast (yellow circle), which was biopsy proven to be a benign fibroadenoma.

pathology in keeping with GIST. A follow-up FDG PET/CT demonstrated expected postsurgical FDG uptake within the resection bed along with persistent uptake within the mediastinum; the latter focus was again reported as concerning for occult metastatic lymphadenopathy (Fig. 2). As no CT correlate had been identified for this mediastinal finding on prior contrast-enhanced CT evaluation, an electrocardiogram (EKG)-gated contrast-enhanced chest CT was obtained. This revealed an enhancing lesion anterior to the left mainstem bronchus and was biopsy proven to be a paraganglioma. Whole body molecular imaging with [^{123}I]-metaiodobenzylguanidine (MIBG) was subsequently performed with no scintigraphic evidence for metastatic disease from the paraganglioma. Given the concurrent presence of these 2 malignancies, genetic analysis was performed demonstrating a mutation within the gene encoding succinate dehydrongenase subunit B (SDH-B), in keeping with CSS.

Discussion

Twenty-five years after Carney first described his eponymous triad, Stratakis and Carney described a separate syndrome of PGL and GIST without the presence of PC [2]. Termed the CSS this disorder has been described in only a handful of patients around the world with the largest study to date including only 5 affected families. Both Carney Triad and CSS are associated with SDH mutations; however, while Carney Triad has been found to be associated with postzygotic epigenetic SDH-C mutations [3,4], familial SDH germline mutations are responsible for CSS. It has been suggested that the disorder is greatly underdiagnosed and may be more common than the Carney triad [5,6].

GISTs are integral to the diagnosis of CSS and Carney Triad, and are mesenchymal tumors found in the stomach and small intestine. While most GIST arise from a mutation in KIT or platelet-derived growth factor receptor alpha, about 7.5% of GISTs have mutations in SDH genes, including those arising as part of the Carney-Stratakis dyad [7]. However, patients with Carney triad have GIST typically caused by mutation in KIT or platelet-derived growth factor receptor alpha and no definite link to SDH mutations [5,8]. Distinguishing Carney Triad from CSS on the basis of clinical findings alone is difficult, as many patients with Carney Triad present with only 2 of the 3 components and their occurrence is often metachronous. Likewise, both syndromes reflect a chronic condition with outcomes largely dependent on the behavior of GIST metastases, regardless of the conventional risk category [9,10]. Despite these similarities, distinguishing patients with CSS from those with Carney Triad has significant implications for the patient and family. While there is a low penetrance of cancer and syndromes in the families of patients with CSS [11,12], there are no reported familial cases of Carney triad. Germline mutations of SDH, as seen in CSS, result in autosomal dominant inherited cancer syndromes with variable clinical presentations and metastatic potential [13]. Therefore, genetic testing provides a definitive diagnosis of CSS and should be utilized for

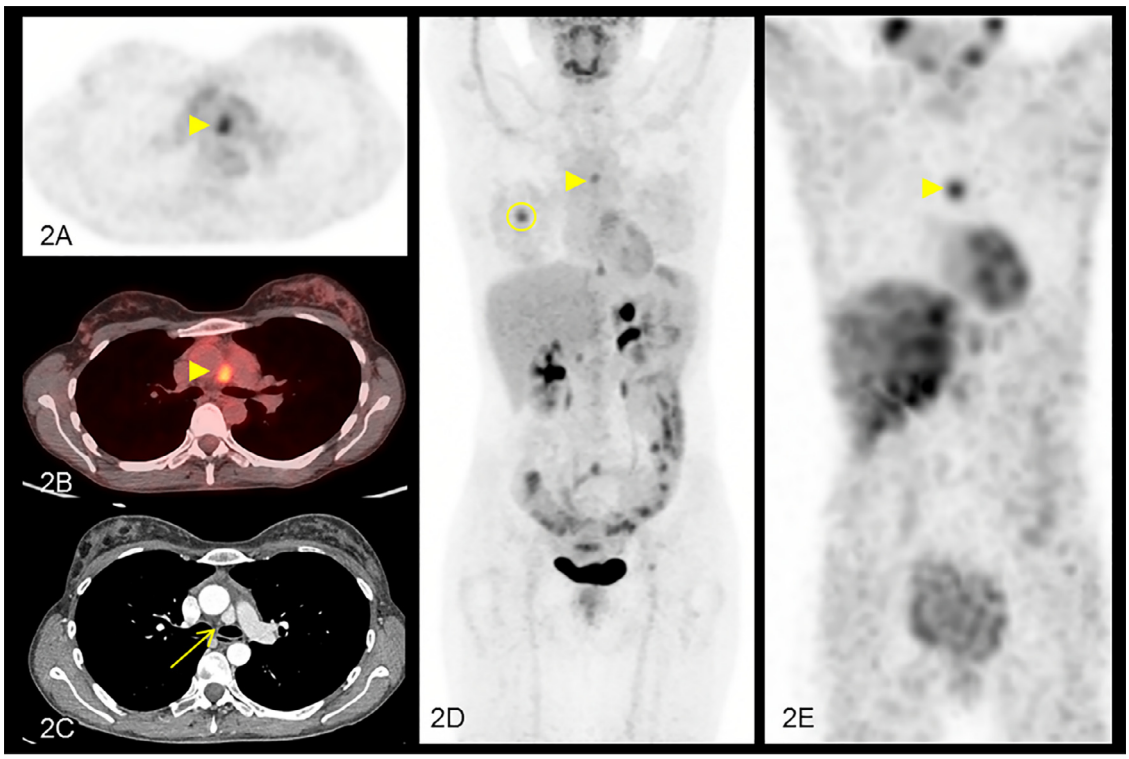

Fig. 2 – Selected images from repeat FDG PET/CT, EKG-gated contrast-enhanced CT, and MIBG SPECT study are shown. Transaxial FDG PET (A) fused PET/CT (B) and EKG-gated contrast-enhanced CT (C) images show the hypermetabolic mediastinal lesion (yellow arrowhead) corresponds to an enhancing soft tissue deposit located in the aorticopulmonary window (thin arrow). Coronal image from the FDG PET MIP (D) demonstrates the persistent mediastinal focus of activity (triangle), as well as the right breast fibroadenoma (circle). Coronal image from the MIBG SPECT MIP (E) demonstrates focal uptake corresponding to the mediastinal paraganglioma (arrow head) and no evidence of metastatic disease.

early detection of the syndrome in immediate family members and descendants [1,5,14].

When identifying paragangliomas, anatomic imaging has an almost 100% sensitivity for adrenal chromaffin tumors, but has a lower accuracy for extra-adrenal disease and in complex disease scenarios, such as CSS [15]. Molecular imaging of paragangliomas with [^{68}Ga]-DOTA-(Tyr^{3})-octreotate (DOTATATE) and MIBG have shown high specificity and sensitivity in identifying sites of primary disease and metastatic spread. While a complete discussion of the genetics that drive paraganglioma development are beyond the scope of this case report, it should be noted that paraganglioma that follow the pseudohypoxic tricarboxylic acid cycle (TCA) cycle pathway, which include those with familial SDH mutations, overexpress the somatostatin receptor, particularly the somatostatin receptor (SSTR) type 2 (SSTR2). DOTATATE targets the SSTR2 receptor with high affinity and affords a near perfect detection rate for primary and metastatic paragangliomas [16]. MIBG continues to have a role in identifying paragangliomas that follow the Kinase signaling pathway, which are found in a separate subset of genetic subtypes including MEN type 2 [17]. While the mediastinal paraganglioma in this case underwent acceptable molecular imaging with MIBG, paragangliomas expressing the SDH mutation are known to have the highest expression of somatostatin receptors, especially SSTR2, and could preferentially have been evaluated with DOTATATE.

Conclusions

This case is noteworthy, not only for the rarity of the diagnosis, but also in its illustration of how a combination of metabolic and focused diagnostic imaging strategies can be used to make subtle diagnoses. Whereas it would be easy to disregard the mediastinal FDG uptake in this case without a correlate on the nongated CT images, a more careful approach using the knowledge of this syndromic association can help identify the potential for malignancy, and lead to further evaluation. In this case, this quest for a definitive answer improved diagnostic outcomes not only for the patient in question, but also potentially for immediate family members or descendants who may share the diagnosis.

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