

Case Report

Succinate dehydrogenase C cardiac paraganglioma: A rare multifocal tumor case with genetic insights

Ahmed Sameer I. Alshaer, MD¹

¹Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

***Corresponding author:**

Ahmed Sameer I. Alshaer,
Department of Medicine, King
Abdulaziz University, Jeddah,
Saudi Arabia.

asalshaier@kau.edu.sa

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ABSTRACT

Cardiac paragangliomas are rare neuroendocrine tumors, accounting for $\leq 1\%$ of primary cardiac tumors. They remain difficult to diagnose, partly because of their nonspecific clinical manifestations and overlapping radiographic features with those of other cardiovascular diseases. This report describes a case of multifocal paragangliomas with pathogenic succinate dehydrogenase C (*SDHC*) gene mutations, highlighting the important role of a combined biochemical, radiographic, and genetic work-up in a multimodal approach. The patient was a 55-year-old man with progressively worsening left-sided tinnitus and hearing loss. Computed tomography scan and magnetic resonance imaging revealed the tumor in the left jugular bulb. In contrast, positron emission tomography with DOTATATE showed highly avid tracer accumulation in both jugular foramina and subcarinal mediastinum, with the former causing minimal indentation of the left atrium. His elevated plasma catecholamine levels (dopamine: 5.11 nmol/L; normetanephrine: 0.72 nmol/L; 3-methoxytyramine: 1.25 nmol/L) were confirmed. After adequate pre- and post-blockade with alpha- and beta-blockers, the patient underwent fractionated stereotactic irradiation of the jugular tumor, in addition to trans-arterial embolization and posterolateral thoracotomy with cardiopulmonary bypass and bovine pericardial reconstruction of the acutely injured left atrium. Histopathological verification demonstrated tumor cells reactive with chromogranin and synaptophysin, with focal necrosis in the heart. Germline genetic testing confirmed pathogenic mutations in the *SDHC* gene. Consequently, he was diagnosed with hereditary paraganglioma.

Keywords: Dopamine secreting tumor, Gallium-68 DOTATATE positron emission tomography-computed tomography, Hereditary paraganglioma syndrome, Multifocal cardiac paraganglioma, Succinate dehydrogenase C mutation

INTRODUCTION

Paragangliomas are rare neuroendocrine tumors arising from extra-adrenal paraganglia of the autonomic nervous system.^[1,2] While most commonly located in the head-and-neck region or along the thoracoabdominal sympathetic chain, cardiac paragangliomas represent a rare subset, accounting for fewer than 1% of primary cardiac tumors.^[1,3] These tumors may arise along the sympathetic chain but are uncommon within the pericardial cavity, where they can involve the atrial or ventricular walls, the coronary sulcus, or the pulmonary arteries.^[1,4] Clinical manifestations range from asymptomatic masses to life-threatening catecholamine excess, arrhythmias, and congestive heart failure due to local invasion.^[1,4,5]

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Furthermore, cardiac paragangliomas are challenging to diagnose due to their non-specific clinical presentations, deep thoracic location, and variable hormonal activity.^[1,4] These hormonally functional neoplasms tend to secrete catecholamines, including dopamine.^[2] In contrast, non-secreting tumors may only be detected during imaging incidentally.^[1] Comprehensive biochemical testing, including plasma metanephrines and 3-methoxytyramine, and functional imaging, such as DOTATATE positron emission tomography (PET), are critical to differentiating these lesions from other mediastinal or cardiac masses.^[1,2,6]

The genetic landscape of paragangliomas has transformed clinical evaluation. Mutations in the succinate dehydrogenase (SDH) complex subunits (SDHA–D and SDHAF2) are key molecular drivers with implications for tumor behavior, malignancy risk, and hereditary predisposition.^[2,3] Although SDHB and SDHD mutations are more commonly associated with multifocal or metastatic disease, SDHC mutations, while rare, are increasingly recognized in hereditary paraganglioma syndromes, as mutations in SDHC have also gradually emerged in cases of hereditary paragangliomas.^[3,7]

This report describes a rare case of multifocal paragangliomas involving the skull base (jugular foramen) and the subcarinal mediastinum, with extension into the left atrium of the heart, in a patient with a pathogenic *SDHC* gene mutation. This report highlights the importance of integrated biochemical, radiologic, and genetic evaluation within a multidisciplinary therapeutic framework in the diagnostic work-up, combined with an interdisciplinary therapeutic strategy.

CASE REPORT

A 55-year-old man with a history of HLA-B27-associated spondyloarthritis, ulcerative colitis well controlled on infliximab, and stage IIIB colon adenocarcinoma in remission was evaluated in 2021. He presented with progressive pulsatile tinnitus. This progressed to left-sided hearing loss by early 2022. Other neurologic and otoscopic examinations were unremarkable.

Initial CT of the temporal bone, obtained in 2023, revealed a 2.5 cm hypervascular mass centered at the left jugular foramen, causing destructive remodeling of adjacent bone and extending into the posterior-inferior tympanic cavity. Subsequently, the magnetic resonance imaging (MRI) demonstrated a vividly enhancing lesion without intracranial extension or brainstem involvement, consistent with a jugular paraganglioma (glomus jugular). Due to the tumor's deep skull-base location and absence of neurologic compromise, an initial conservative approach with observation and symptomatic management was adopted.

During the next year, the patient experienced intermittent symptoms of anxiety, flushing, positional dizziness,

and headaches, which could represent an excess of catecholamines in functional paragangliomas. Later in 2023, surveillance imaging revealed a new subcarinal mediastinal mass of 2.7 cm. There was also some minimal indentation of the posterior wall of the left atrium detected by thoracic MRI, suggesting possible cardiac involvement.

An extensive biochemical work-up was conducted in early 2024 due to multifocal involvement. Plasma analysis revealed elevated levels of dopamine and 3-methoxytyramine, with a borderline elevation of normetanephrine. Twenty-four-hour urinary levels of catecholamines confirmed the elevation of dopamine, normetanephrine, and 3-methoxytyramine. ⁶⁸Ga-DOTATATE PET-CT showed high uptake of somatostatin receptors in both lesions, with no evidence of metastatic disease. Genetic counseling was pursued, and next-generation sequencing identified a pathogenic SDHC mutation, confirming hereditary paraganglioma-pheochromocytoma syndrome. Given tumor functionality, proximity to cardiac structures, and inherited risk, a multidisciplinary tumor board recommended a staged treatment approach prioritizing patient safety and long-term surveillance.

Assessment

Plasma catecholamine analysis demonstrated markedly elevated dopamine (5.11 nmol/L; reference ≤ 0.13) and elevated 3-methoxytyramine (1.25 nmol/L; reference ≤ 0.29), with borderline elevation of normetanephrine, consistent with a functional dopamine-secreting paraganglioma. The increased levels of dopamine and 3-methoxytyramine are characteristic biochemical markers of head and neck paragangliomas and SDH mutated tumors as shown in Table 1. Excess dopamine, normetanephrine, and 3-methoxytyramine were found in the 24-h urine samples.

High-resolution CT and MRI of the skull base identified a 2.5-cm hypervascular jugular foramen mass with bony erosion and avid contrast enhancement imaging features typical of paraganglioma, as shown in Figure 1. Thoracic MRI demonstrated a 2.7-cm posterior mediastinal lesion abutting the posterior wall of the left atrium, without definite myocardial invasion.

While ⁶⁸Ga-DOTATATE PET-CT revealed intense somatostatin receptor avidity in both lesions and no evidence of additional disease, supporting DOTATATE PET as the preferred imaging modality for well-differentiated paragangliomas and pheochromocytomas.

Given multifocal disease and biochemical functionality, germline genetic evaluation was undertaken and confirmed a pathogenic SDHC variant, establishing hereditary paraganglioma-pheochromocytoma syndrome. First-degree relatives were referred to for genetic counseling and cascade testing.

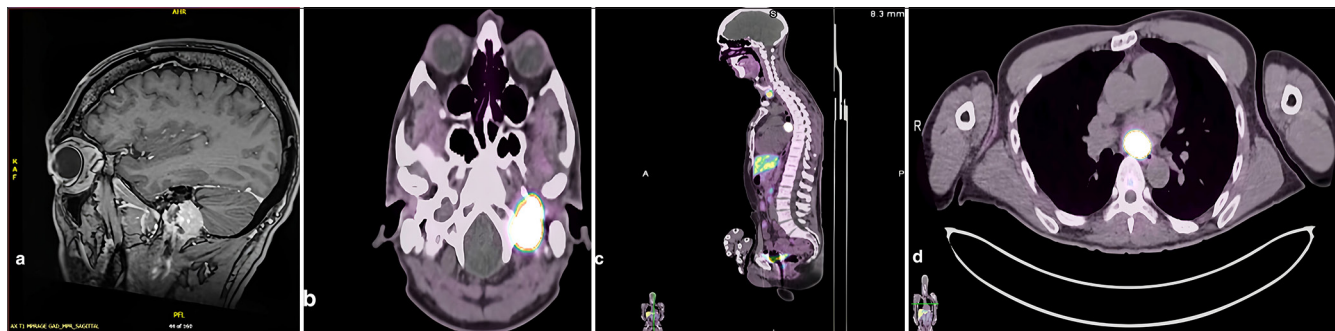


Figure 1: A 55-year-old man with multifocal paragangliomas involving the skull base and mediastinum. (a) Sagittal post-contrast magnetic resonance imaging shows an enhancing mass centered at the left jugular foramen. (b) Axial 68Ga-DOTATATE positron emission tomography-computed tomography (PET-CT) demonstrates somatostatin-receptor-avid left jugular foramen lesion. (c) Sagittal 68Ga-DOTATATE PET-CT reveals a subcarinal lesion with mild indentation of the left atrium. (d) Axial 68Ga-DOTATATE PET-CT confirms an avid subcarinal paraganglioma abutting the posterior left atrial wall.

Table 1: Biochemical evaluation demonstrating dopamine-secreting paraganglioma.

Biomarker	Plasma level (nmol/L)	Reference range (nmol/L)
Dopamine	5.11 nmol/L	≤0.13 nmol/L
Normetanephrine	0.72 nmol/L	≤0.89 nmol/L
Metanephrine	0.15 nmol/L	≤0.49 nmol/L
3-Methoxytyramine	1.25 nmol/L	≤0.29 nmol/L

Treatment

Management required a multidisciplinary approach involving endocrinology, radiation oncology, interventional radiology, cardiology, cardiothoracic surgery, and clinical genetics.

In view of the potential hemodynamic instability induced by the catecholamines, alpha blockade with doxazosin was started 7–14 days pre-operatively, followed by beta-blockade with metoprolol. This treatment protocol involves current recommendations in the management of paragangliomas. These recommendations include those proposed by the Endocrine Society.^[2] Adequate hydration and electrolyte monitoring were maintained throughout the preparation period.

Regarding the management of skull-base lesions, given the deep skull-base location of the jugular foramen tumor and the risk of cranial nerve morbidity with surgical resection, fractionated stereotactic radiotherapy (FSRT) was selected as the primary treatment modality in May 2024. FSRT is a well-recognized approach for head-and-neck paragangliomas where surgical morbidity is high.

While preparation for mediastinal lesion resection and due to hypervascularity and proximity to the left atrial wall, preoperative bronchial artery embolization was performed to reduce intraoperative bleeding and facilitate safe tumor excision by August 2024.

Two-week post-embolization, the subcarinal mass was resected through right posterolateral thoracotomy under cardiopulmonary bypass. *En bloc* resection was achieved, and the involved left atrial wall was reconstructed using bovine pericardium. This operative strategy parallels reported experiences in specialized centers managing cardiac paragangliomas involving the atrial myocardium.

The patient developed tachy-brady syndrome postoperatively, attributed to atrial manipulation and conduction system irritation. A dual-chamber pacemaker was implanted, with good recovery, thereafter, as illustrated in the post-operative course for this case.

Outcome and follow-up

There were no complications in the immediate post-operative period, and the patient showed no evidence of bleeding, cardiac tamponade, or heart failure. Hemodynamics remained stable, allowing a gradual tapering in antihypertensive medications. Histology revealed the tumor to be a paraganglioma, with characteristic zellballen patterns. Tumor cells were positive for chromogranin and synaptophysin, and sustentacular cells were identified with S-100 staining. There was necrosis attributed to pre-operative embolization. Margins and lymphovascular invasion were free.

Transthoracic echocardiographs showed preserved biventricular function and intact atrial pericardial patches. Review of the pacemaker data confirmed normal pacemaker function. Biochemical studies revealed normalization of urinary dopamine and 3-methoxytyramine levels, indicating biochemical control, on 3 to 6 months of serial follow-up. Interval DOTATATE PET-CT at 6 months confirmed tumor resolution and stable disease in the previously treated jugular lesion as shown in Figure 2.

DISCUSSION

Paragangliomas arise from extra-adrenal paraganglia, frequently along the sympathetic chain.^[2] This case is notable for multifocal skull-base and thoracic disease with cardiac extension associated with a pathogenic rare SDHC mutation.^[3,7] Although head and neck paragangliomas are often non-functional, catecholamine excess may occur, necessitating biochemical evaluation even when lesions are presumed silent.^[1,2,6]

Cardiac paragangliomas are exceedingly uncommon, accounting for $\leq 1\%$ of primary cardiac tumors, and most often involve the left atrium, atrioventricular groove, or pulmonary artery. Clinical presentations range from palpitations and syncope to hypertensive crises.^[1,3,4] These symptoms in our patient, including anxiety, headaches, and positional dizziness, were most likely attributable to excessive catecholamine secretion, reflecting the often-insidious clinical presentation.^[1,2,5]

The biochemical profile (dopamine/3-MT predominant) is characteristic of head-and-neck tumors and is strongly associated with SDH mutations.^[2,3,6] 3-Methoxytyramine (3-MT) is particularly sensitive for detecting dopamine-producing pheochromocytomas and paragangliomas (PPGL) and may be elevated even with minimal norepinephrine/epinephrine secretion.^[2,6]

Genetic testing is central to PPGL care. SDH-PPGL syndromes show genotype and phenotype differences among SDH genes, notably between the rarer SDHC-related disease and the more common SDHB and SDHD syndromes. The penetrance of SDH related PPGL is incomplete and variable,

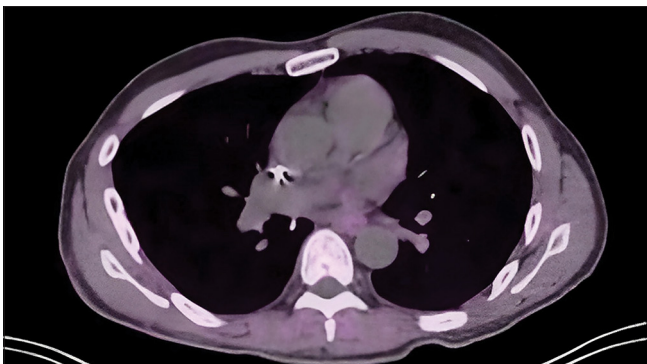


Figure 2: Six-month post-treatment axial contrast-enhanced computed tomography image shows no residual or recurrent subcarinal paraganglioma and an intact atrial reconstruction site. Due to the patient's known genetic mutation of succinate dehydrogenase C, along with his lifetime risk of multifocal and recurrent disease, ongoing surveillance was recommended, such as ⁶⁸Ga-DOTATATE positron emission tomography-computed tomography and whole-body Magnetic resonance imaging. Genetic counseling was also offered to first-degree relatives.

whereas data on SDHC mutation carriers are limited but indicates a lower penetrance than SDHD related disease.^[8-11] The SDHC related disease appears to be characterized mainly by non-metastatic head and neck paragangliomas, with lower rates of tumor multiplicity and malignant transformation.^[2,3,7]

The variations of genotypes have direct implications for family screening. The consensus recommendations for biochemical and imaging surveillance are broadly similar across SDH mutations.^[8,12] Beyond PPGL, SDH mutations are also associated with other malignancies, particularly gastrointestinal stromal tumors (GIST) and renal cell carcinoma (RCC).^[13] Recurrent SDHC epimutations, largely somatic, are characteristic of GIST and Carney triad.^[13]

⁶⁸Ga-DOTATATE PET-CT offers superior sensitivity and specificity for well-differentiated PPGLs compared with MIBG or FDG and is preferred for staging and surveillance.^[1,6]

FSRT can control skull-base paragangliomas while minimizing cranial nerve injury,^[1] whereas pre-operative embolization of hypervascular intrathoracic lesions adjacent to the heart reduces bleeding risk and facilitates resection.^[1,14] Definitive resection with cardiopulmonary bypass and atrial patch reconstruction has been reported with favorable outcomes in specialized centers.^[14-17] In unresectable or metastatic disease, treatment options include external-beam radiation, peptide receptor radionuclide therapy, and temozolomide.^[1]

Arrhythmias, including tachy-brady syndrome, may occur following atrial manipulation; prompt pacemaker implantation restores hemodynamic stability.^[14] Given SDHx mutation status, lifelong surveillance with periodic imaging and annual biochemical testing is recommended.^[2,3]

Cardiac paragangliomas are exceptionally rare; functional assessment is essential even when lesions appear clinically non-secretory. Comprehensive biochemical testing should include plasma and urinary dopamine, normetanephrine, and 3-methoxytyramine. Elevation in 3-methoxytyramine is a sensitive indicator of dopamine-secreting PPGL, particularly in SDHx-associated tumors. SDHC mutations, although less common than SDHB or SDHD variants, are linked to hereditary paraganglioma syndromes and may be present with multifocal disease. Genetic testing is critical for diagnosis, prognostication, and cascade family screening. ⁶⁸Ga-DOTATATE PET-CT is the preferred imaging modality for staging and surveillance of somatostatin receptor-positive PPGLs. Preoperative alpha-adrenergic blockade and, when indicated, selective tumor embolization are key strategies to mitigate intraoperative catecholamine surges and bleeding risk. Left-atrial paragangliomas can be safely resected using cardiopulmonary bypass and atrial wall reconstruction in experienced cardiac centers. Lifelong

surveillance is mandatory in SDHx mutation carriers, incorporating annual biochemical testing and periodic whole-body imaging due to the risk of recurrence or new tumor development. Optimal outcomes require coordinated multidisciplinary management, including endocrinology, cardiology, cardiothoracic surgery, radiation oncology, genetics, and interventional radiology.

Limitations of the study

The main limitation of this study is its single-case design. Furthermore, the short follow-up period precludes evaluation of long-term recurrence risk and SDHC related disease behaviour.

CONCLUSION

This represents a complex situation with multiple paragangliomas involving the heart in the context of an SDHC pathogenic variant, highlighting the complexities of diagnosis and treatment in hereditary cases of PPGL. With successful involvement of multidisciplinary approaches, including complex functional imaging, targeted external beam, pre-operative embolization, and cardiothoracic surgery, the patient gained improvements in the symptoms, biochemical control, and no residual or recurrent subcarinal paraganglioma on imaging. This case underscores the central contribution of genetic analysis in the identification of hereditary tumor syndromes and in designing surveillance approaches. There also exists an obvious need for enhanced clinical awareness in high-risk and anatomically complex presentations such as parasympathetic tumors involving the heart in unusual cases.

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