Sympathetic paraganglioma in the pericardium with paraganglioma syndrome 3: Multimodality imaging findings

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To the Editor: Sympathetic paraganglioma in the pericardium is rare, which can be life-threatening. It presents with symptoms, such as refractory hypertension, palpitations, and other hormone-related manifestations. This study presented a unique case of type 3 paraganglioma originating from the mediastinum, accompanied by multimodality imaging findings, including computed tomography (CT) scan, ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT), ^{68}Ga-DOTA-1-Nal3-octreotide positron emission tomography/CT (^{68}Ga-DOTANOC PET/CT), and ^{18}F-fluorodihydroxyphenylalanine positron emission tomography/CT (^{18}F-FDOPA PET/CT).

A 54-year-old woman, presenting with a 1-month history of fever and cough, particularly during afternoon, was admitted to Guangdong Provincial People's Hospital. All clinical data related to the patient were collected with the consent of the patient and this study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (NO. KY2023-1031-01). The patient reported recurring headaches and palpitations, especially during emotionally charged situations. Contrast-enhanced computed tomography (CECT) demonstrated a mass of about 6.7 cm × 5.2 cm above the left atrium in the mediastinum. The mass exhibited uneven enhancement and rich blood supply, with distorted vessels found at its periphery, which was suspected to be a metastatic tumor [Figure 1A–C]. Subsequently, the patient underwent ^{18}F-FDG PET/CT scan to evaluate tumor aggressiveness and proliferation. The results revealed multiple areas of high ^{18}F-FDG uptake, not only within the mediastinal tumor but also in adipose tissue surrounding the trachea, paraspinal area, and both the shoulder and neck [Figure 1D–F]. The presence of activated brown adipose tissue (BAT) suggested a neuroendocrine origin for the tumor, which was further supported by its catecholamine-secreting function.

The patient subsequently underwent ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDOPA PET/CT, which revealed positive somatostatin receptor (SSTR) expression [Figure 1G–I] and strong positive catecholamine metabolism [Figure 1J–L] within the mediastinum, specifically in the pulmonary artery-left atrial space.

Following this, the levels of metanephrine and normetanephrine (MNs) were measured, revealing elevated plasma levels of normetanephrine (3.64 nmol/L, normal range ≤0.90 nmol/L) and 3-methoxytyramine (6.46 nmol/L, normal range <0.18 nmol/L). Additionally, elevated urinary vanillylmandelic acid level was detected. Next-generation sequencing identified a pathogenic mutation (loss of heterozygosity) in the *SDHC* gene (1q23.3). Consequently, the clinical diagnosis was determined to be sympathetic paraganglioma with paraganglioma syndrome 3 originating from the pericardium.

Due to the tumor's abundant blood supply and its proximity to the pulmonary artery and left atrium, surgical intervention was considered high-risk. Consequently, the patient underwent treatment involving an alpha receptor blocker, long-acting somatostatin, and three cycles of transcatheter arterial embolization (TAE) using polyvinyl alcohol (PVA) granules. This regimen led to a significant reduction in plasma levels of MNs. Plasma normetanephrine level was normalized, whereas 3-methoxy tyramine level was reduced by 84% (from 6.46 nmol/L to 1.02 nmol/L) over the course of treatment. Upon follow-up, ^{18}F-FDG PET/

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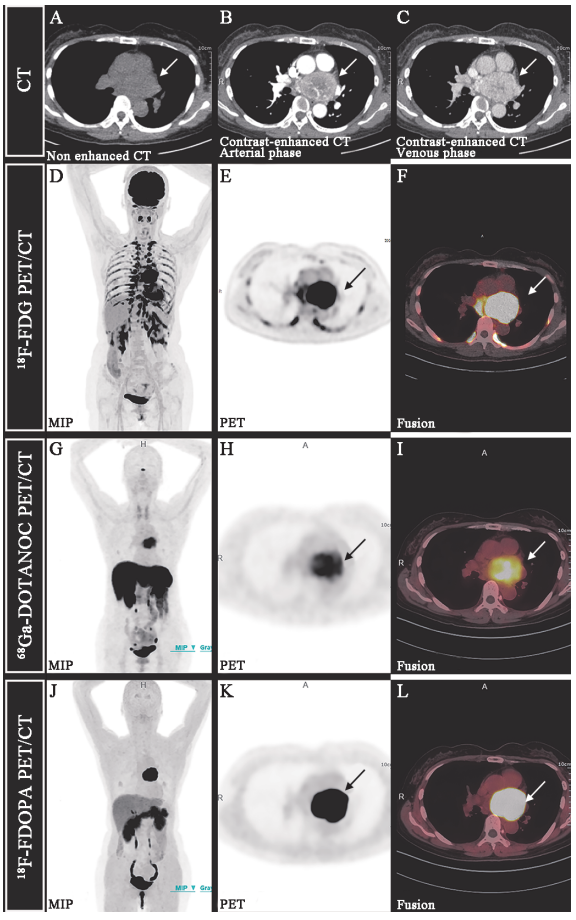

Figure 1: Unclear boundaries in the mediastinum (A, arrowhead). Abundant blood supply during the arterial phase (B, arrowhead). Significant enhancement during the venous phase (C, arrowhead). High accumulation of ^{18}F-FDG in the mass and the BAT in the peritracheal, paraspinal, shoulder, and neck spaces bilaterally (D). ^{18}F-FDG in the axial view of selected PET (E) and fused PET/CT (F). Strong positive SSTR (G–I) and catecholamine metabolism (J–L). ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; BAT: Brown adipose tissue; CT: Computed tomography; MIP: Maximum intensity projection; PET: Positron emission tomography; SSTR: Somatostatin receptors.

CT scan revealed no increase in BAT uptake, and the size of tumor lesion was significantly reduced [Supplementary Figure 1, http://links.lww.com/CM9/C159].

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors characterized by catecholamine production. They arise from the adrenal medulla and extra-adrenal ganglia located in the thorax, abdomen, pelvis, and neck. Approximately 10% of pheochromocytoma and 20% of paraganglioma cases progress to metastatic disease, with a corresponding 5-year survival rate of approximately 50%.[1] Notably, some PPGLs may present without typical clinical symptoms, emphasizing the critical importance of early detection in clinical management.

Recently, several studies have highlighted the increased activation of BAT in PPGLs. ^{18}F-FDG uptake in BAT may resemble metastases in the neck and mediastinum. Furthermore, it has been reported that detecting BAT activity on ^{18}F-FDG PET/CT in PPGL patients, especially those with *SDHx* mutation, is associated with a higher mortality rate and unfavorable survival outcomes.[2]

SSTRs are abundantly expressed on various neuroendocrine tumor (NET) cells, serving as viable targets for radionuclide imaging and therapy. Radionuclide-labeled somatostatin can specifically bind to SSTRs on the tumor cell membranes, facilitating accurate tumor localization and diagnosis with the aid of radioactive isotopes. Among the most commonly utilized SSTR-targeting peptides for PET/CT imaging of neuroendocrine neoplasms are ^{68}Ga-DOTA-conjugated peptides, such as ^{68}Ga-DOTA-d-Phe1-Tyr3-octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-DPhe1-Tyr3-octreotate (^{68}Ga-DOTATATE), and ^{68}Ga-DOTANOC.[3]

Dihydroxyphenylalanine (DOPA) acts as a precursor for endogenous catecholamines. ^{18}F-FDOPA, functioning as a DOPA analog, serves as a radiotracer targeting catecholamine metabolism. The approval of ^{18}F-DOPA PET/CT for diagnosing and localizing tumors harboring a succinate dehydrogenase D variant gene mutation has been pivotal.[3,4]

PPGLs notably express high levels of SSTRs, particularly subtypes 2, 3, and 5. ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE PET/CT have demonstrated exceptional accuracy in lesion-based diagnosis among patients with PPGLs. Previous research indicated sensitivity of 97.4% for diagnosing pheochromocytoma (PCC) and 95.8% for paraganglioma (PGL) using ^{68}Ga-DOTATATE PET/CT, surpassing other functional imaging methods, such as CT/MRI, ^{18}F-DOPA, ^{18}F-FDOPA, and ^{18}F-FDG.[5] However, in this case, strong positive catecholamine metabolism was found in ^{18}F-DOPA PET/CT. This change may be related to the *SDHC* gene mutation and the predominant secretion of 3-methoxy tyramine in the tumor.

Positive imaging with SSTRs suggests the potential use of somatostatin analogs (SSAs) and peptide receptor radionuclide therapy (PRRT) for treating metastatic PPGLs.[3] In this particular case, the patient underwent a ^{68}Ga-DOTANOC PET/CT examination, which revealed positive SSTR expression and strong positive catecholamine metabolism in the mediastinum. However, experience with PRRT for treating complex and large sympathetic paragangliomas in the mediastinum is relatively limited, and the treatment is expensive. As an alternative, the patient underwent three cycles of TAE using PVA while receiving alpha-blocker and long-acting somatostatin treatment. This approach resulted in a significant reduction in plasma metanephrines concentration, a decrease in tumor volume, and the disappearance of ^{18}F-FDG uptake by BAT.

In conclusion, the activation of BAT and the utilization of multimodal imaging techniques significantly contribute to the diagnosis and differential diagnosis of mediastinal paragangliomas.

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