



Multimodality Imaging Appearance of Intrapericardial Paragangliomas

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Abstract

Paragangliomas are neuroendocrine tumors of the sympathetic and parasympathetic nervous system that originate from neural crest cells. Less than 1% of paragangliomas are found in the heart, originating from intrinsic cardiac ganglia cells in the posterior wall the atria, atrioventricular groove, and along the root of the great vessels. A 10-year review of our institution's database identified nine patients who had documented intrapericardial paragangliomas. We describe the multimodality imaging appearance of these tumors. The most common findings include embedment and wrapping around the great vessels and atrioventricular groove within the confines of the pericardium, markedly avid heterogeneous enhancement, distinct engorged neovascularization, and in large lesions, central low attenuation areas compatible with hemorrhage, necrosis, or cystic degeneration.

Keywords

- ▶ chest imaging
- ▶ intrapericardial paragangliomas
- ▶ multidetector computed tomography

Key Messages

1. Intrapericardial paragangliomas are rare endocrine tumors with consistent multimodality imaging appearances.
2. Common features of these tumors are encasement and wrapping of the roots of the great vessels and atrioventricular groove, markedly avid intravenous (IV) contrast enhancement, and surrounding serpiginous structures.
3. When at least two of these three elements mentioned are observed, the possibility of a paraganglioma should be strongly suggested in the differential diagnosis of a hypervascular mass, despite their rare occurrence.

Introduction

Paragangliomas are endocrine tumors derived from neural crest cells, which migrate with cranial nerves, great vessels, autonomic nerves, and ganglia during embryonic development. Consequently, these tumors may be found along the parasympathetic nerves of the head, neck or mediastinum, sympathetic prevertebral chains, and nerves of pelvic and retroperitoneal organs. Approximately 1 to 2% of paragangliomas occur within the chest and tend to be in the posterior mediastinum. Less commonly, the tumor may be in or around the heart.^{1–3} These tumors arise from intrinsic cardiac ganglia cells located in the posterior wall of the atria,

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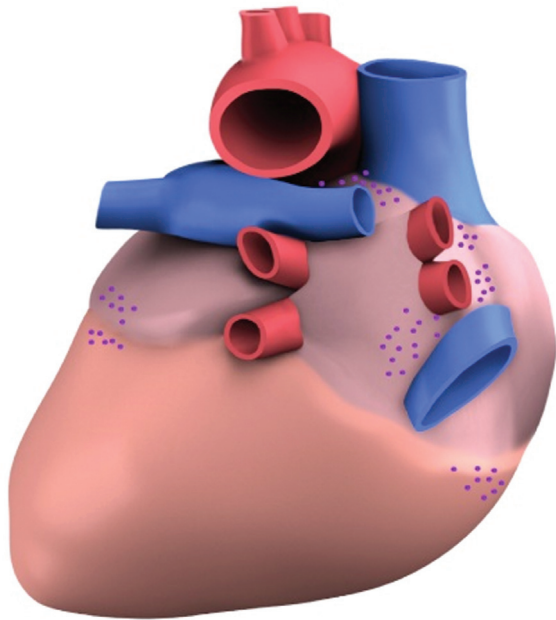


Fig. 1 Human pericardial neural plexus. The dots represent the location of the neural crest cells. The intrinsic cardiac ganglia cells are in the posterior wall of the atria, left greater, in the atrioventricular groove, and along the root of the great vessels.

atrioventricular groove, and along the roots of the great vessels (►Fig. 1). This location accounts for less than 1% of all primary cardiac tumors.⁴ However, the estimate may not be accurate, since some of these tumors may be found incidentally and no large autopsy series are available. Our aim was to describe the multimodality imaging features of all patients with the final diagnosis of intrapericardial paragangliomas presenting at our institution between 2009 and 2018.

Materials and Methods

An Institutional Review Board institutionally approved retrospective search of patients with pathologically proven aorticopulmonary/intra-pericardial paragangliomas was performed at our institution between 2009 and 2018. A review of their pertinent imaging studies was performed, including multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), 18-fluorine positron emission tomography-computed tomography (PET-CT), and iodine-131 meta-iodobenzylguanidine single-photon emission computed tomography/computerized tomography (MIBG-SPECT) scans, with special emphasis on the more commonly performed MDCT studies.

Results

Our search yielded 9 patients with documented intra-pericardial paragangliomas: two female patients and seven male patients. The age of presentation ranged from 15 years of age to 71 years of age with a mean age of 48 years. One patient carried a family history of paraganglioma with a succinate

dehydrogenase (SDH) gene mutation known to predispose to these tumors. The remaining were sporadic paraganglioma cases. Of these, one patient was asymptomatic. Four underwent evaluation related to tumor compression or atypical chest pain. Two other patients were discovered during routine restaging imaging for melanoma and colon cancer, respectively. One patient with a catecholamine-producing tumor was found to have uncontrollable hypertension with elevated metanephrines in blood and urine. The patient's detailed demographics, clinical information, and outcomes are summarized in ►Supplementary Table S1 (online only).

Multimodality Imaging Findings

In most patients, the tumor characteristics were strikingly similar independent of their functionality. All patients had MDCT contrast studies that allowed for an accurate depiction of their anatomic location and degree of infiltration. Additionally, two patients had 18-fluorine PET/CT, two patients had MRI scans, and one patient had MIBG SPECT. The lesions were variable in size from 3 to 11 cm in diameter with an average of 7 cm. Medium and large sized tumors had a heterogeneous appearance and the smaller tumors were predominantly homogeneous (►Fig. 2). All cases had markedly avid IV contrast enhancement and visible surrounding serpiginous vessels. The invasive characteristics were adequately documented on MDCT or MRI. A seemingly consistent feature of large tumors was wrapping around the roots of the great vessels (within the confines of the pericardium) and atrioventricular groove without significant constriction of the neighboring vasculature (►Figs. 3, 4). The lesions greater than 3 cm in size demonstrated central low attenuation due to hemorrhage, necrosis, or cystic degeneration (►Figs. 4, 5). The MRI findings included iso- or hypointensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images in relationship to the myocardium. Within the substance of the tumor, suggestion of hypervascularity even in the noncontrast sequences was

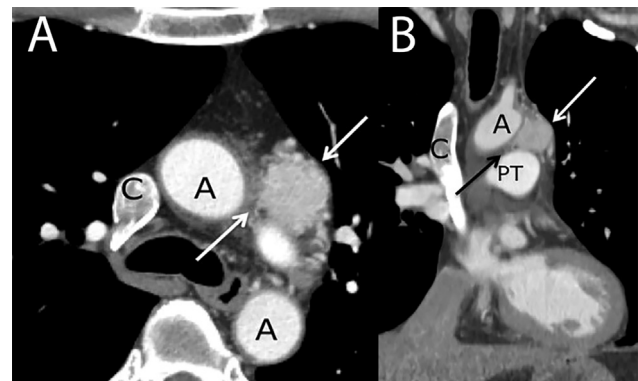


Fig. 2 Patient 2: A 71-year-old male with an incidentally discovered mediastinal mass. Postcontrast multidetector computed tomography. (A) Axial image and (B) coronal image. A predominantly homogeneous hypervascular tumor with somewhat irregular contour occupies the anteroposterior window (arrows). The perivascular separation fat plane was preserved, and no invasion was noted. Several small serpiginous vessels are demonstrated surrounding the lesion. Note flow artifact in the superior vena cava (C), aorta (A), and pulmonary trunk (PT).

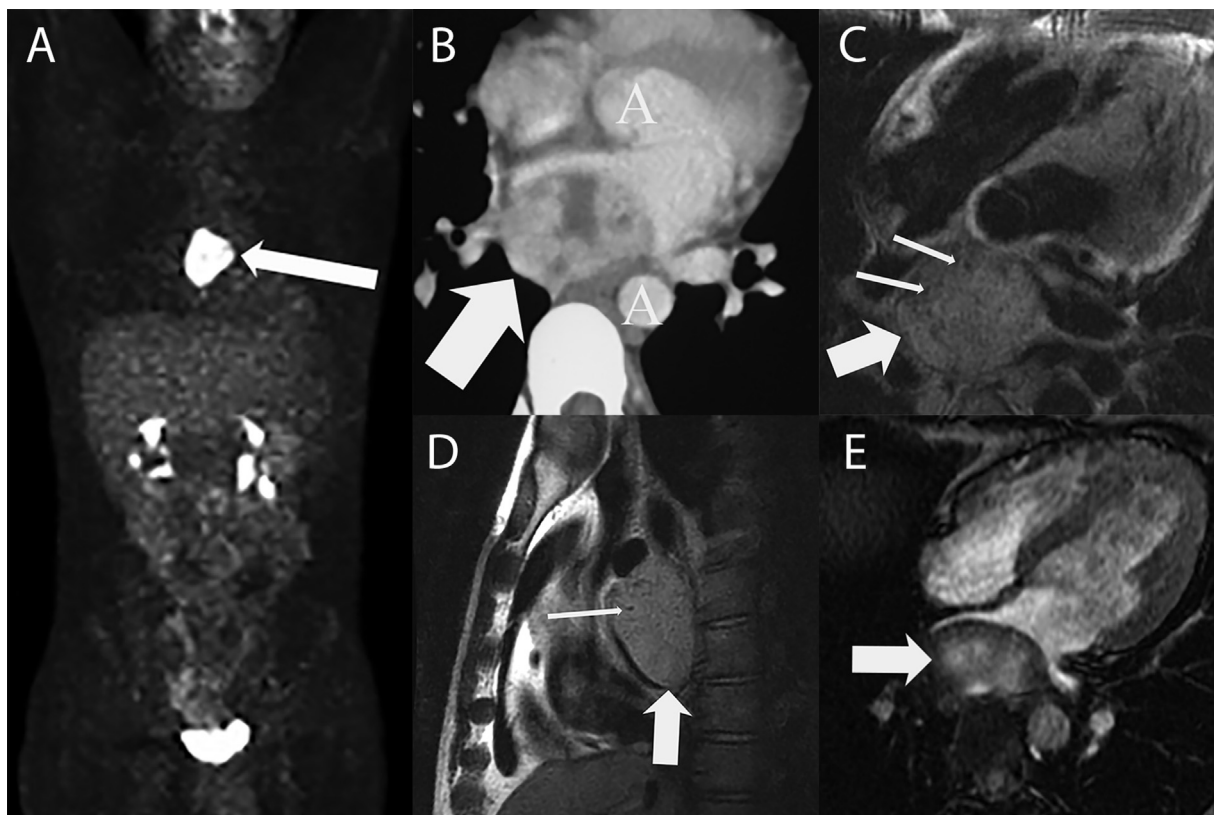


Fig. 3 Patient 5: A 54-year-old male with uncontrollable hypertension with intrapericardial paraganglioma. (A) The coronal iodine-131 metaiodobenzylguanidine scan shows intense radiotracer uptake (white thick arrow). (B) Postcontrast multidetector computed tomography axial image. The large hyperenhancing tumor is in close proximity to the left atrial wall. (C) and (D) noncontrast gradient echo T1-weighted axial and sagittal images, respectively. The mass is isointense to muscle with multiple flow voids suggesting its vascular nature. (E) Steady-state free precession axial image demonstrates the heterogeneous signal with areas of high signal, presumed cystic degeneration, or necrosis. Infiltration at the dome of the left atrium was suspected and confirmed on surgical exploration. After a second attempt to resect residual tumor, the patient succumbed from massive hemorrhage. Aorta (A).

seen in the T1-weighted MRI images with prominent “flow voids” (►Fig. 3). Pericardial effusion was distinctively absent in most patients, except for patient no 3 in which recent resection was attempted (►Supplementary Table S1 [online only]).

Discussion

Tumor Definition

According to the World Health Organization 2004 classification system, the term paraganglioma encompasses both extra-adrenal sympathetic and parasympathetic tumors independent of their functional status.^{5,6} Typically parasympathetic paragangliomas tend to be nonfunctional with less than 5% producing catecholamines,⁷ whereas the sympathetic counterpart is similar to adrenal pheochromocytomas and is usually functional.⁸

Paragangliomas may present sporadically or may be linked to genetic factors including germ line mutations such as multiple endocrine neoplastic type 2 types A and B, Von Hippel Lindau, neurofibromatosis type 1, hereditary paraganglioma syndrome, Carney-Stratakis dyad (paraganglioma and gastrointestinal stromal tumor [GIST]), Carney triad (paraganglioma, GIST, plus pulmonary chondroma), and SDH mutations.⁸

According to recent discoveries, a little over 20% of patients presenting with presumed sporadic tumors have genetic mutations associated with familial pheochromocytomas and paragangliomas. This challenges the traditional notion of the “10 percent rule”: 10% familial, 10% malignant, and 10% extra-adrenal. The tumor location and the risk of malignancy also depend on the specific genetic abnormality.⁹

Unfortunately, benign paragangliomas cannot be distinguished from the malignant type histologically.⁸ There is no accepted staging classification, and the treatment is based on whether locoregional invasion or metastases have occurred. Metastatic disease tends to be seen more commonly with extra-adrenal paragangliomas.^{10,11}

Intrapericardial tumors arising from the ganglia associated with the aorta, pulmonary arteries, or coronary arteries are also referred to as aorticopulmonary paragangliomas. In a recent retrospective case review, this variety was found to be the more common with an incidence of ~69% compared with 31% for intracardiac tumors.¹² Most of the true intracardiac tumors involve the left atrium followed by the right atrium. Other locations such as the left ventricle or interatrial septum are extremely rare.^{12–16} Both functional and nonfunctional paragangliomas have been described in and around the heart, although nonfunctioning tumors appear to be more common.¹⁷

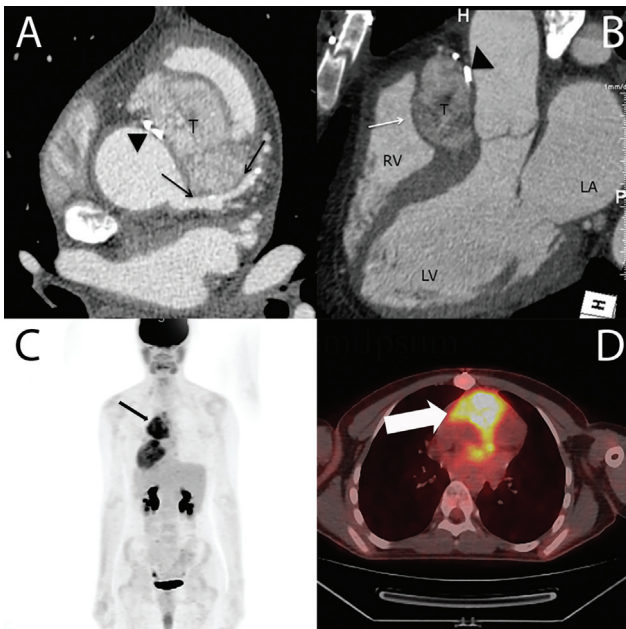


Fig. 4 Patient 7: Intrapericardial paraganglioma in a 63-year-old male with a history of rectal cancer. Postcontrast multidetector computed tomography: (A) axial image and (B) coronal oblique image. A heterogeneously enhancing mass is seen in the area of the aorticopulmonary window abutting the left main and proximal left anterior descending coronary arteries (black arrows in A). Eccentric surgical clips from a previous open biopsy (arrowheads). Small arrows point at prominent serpiginous surrounding vessels. (C) Coronal three-dimensional maximum intensity projection fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) and (D) fusion axial FDG-PET/CT images show the hypermetabolic nature of the tumor (arrows). Tumor (T), right ventricle (RV), left atrium (LA), left ventricle (LV).

Histopathology

The cytology and histologic pattern of paragangliomas are variable. The typical so-called “zellballen” pattern manifested by nests of uniform polygonal cells is not always seen. Spindle cells, mixtures of large and small cells, and extreme cytologic atypia may be found.⁸

A generic neuroendocrine marker, chromogranin A, is reliable in distinguishing pheochromocytomas and other paragangliomas from tumors that are not neuroendocrine. Tumors are often also positive for tyrosine hydroxylase, a rate limiting enzyme in catecholamine biosynthesis. The classic histologic pattern from the lesion found on patient no 9 of our case series is depicted in ►Fig. 6.

Clinical Presentation

Tumors secreting catecholamines may cause hypertension, headaches, sweating, syncope, dyspnea, cough, and weight loss. Nonfunctioning tumors may significantly enlarge before they manifest by their exerting mass effect on adjacent structures. Symptoms of heart failure, ischemia due to vascular compression and obstruction of systemic, pulmonary, or coronary blood flow may occur.^{12,18}

The significant morbidity and mortality from extra-adrenal paragangliomas are derived not only from the

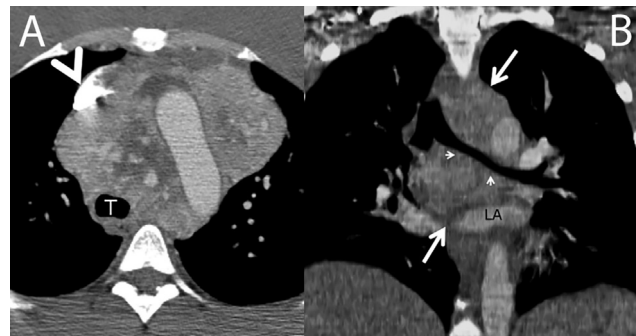


Fig. 5 Patient 4: Paraganglioma in a 32-year-old male with progressive dyspnea. (A) Postcontrast multidetector computed tomography (MDCT) axial image. Note the large heterogeneous highly vascular middle mediastinal mass on both sides of the aortic arch. There is abutment and mild compression of the superior vena cava (arrowhead) and posterior displacement of the trachea (T). (B) Coronal postcontrast MDCT image. The mass (large arrows) abuts the roof of the left atrium (LA) and narrows the left mainstem bronchus (short arrows).

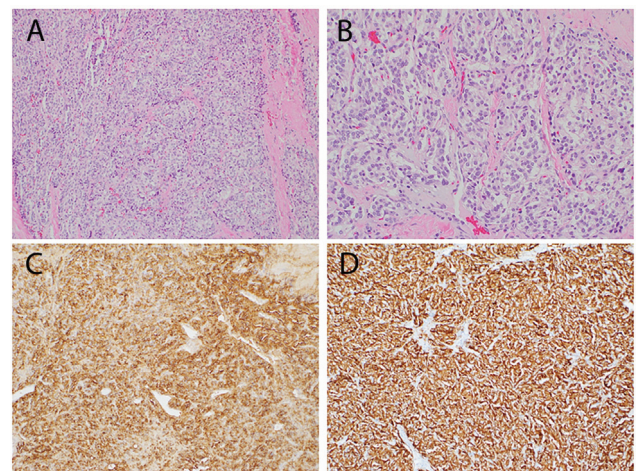


Fig. 6 (A-B) Hematoxylin and eosin 100x and 200x, respectively: Nested neoplastic proliferation of bland-appearing tumor cells with delicate capillary meshwork and low mitotic activity. (C-D) By immunohistochemistry 200x, tumor cells are positive for chromogranin and synaptophysin, respectively. Not shown, tumor cells were positive for CD56 and S100 immunostain highlighted sustentacular cells.

cardiovascular effects of the catecholamine production but also depend on the degree of invasiveness.⁷ Associated symptoms vary according to size, location, and functionality of the tumor. In a retrospective case review series, invasiveness and functionality of paragangliomas were more commonly found in the mid-fourth decade of life, whereas nonfunctional inactive tumors occurred around the mid to late fifth decade.¹²

Management

In patients with primary cardiac paragangliomas, surgical resection with disease-free margins is the only opportunity of cure. The lesion excision is usually challenging, due to the nature of the tumor infiltration and extreme vascularization. The tumors often parasitize blood flow from branches of the

coronary arteries. Hence, treatment planning requires gathering detailed information as to the extent of spread into surrounding tissue and accurate evaluation of the blood supply.⁵

Resection of tumors that extend into the atrioventricular groove, directly involve the coronaries, or extend into the left ventricle, is associated with high morbidity and may require autotransplantation and extensive cardiac reconstruction.^{2,13,14} In cases with aggressive invasion, allotransplantation should be considered. Tumor burden can be reduced with palliative surgery and systemic chemotherapy agents such as 131I-Metaiodobenzylguanidine (131I-MIBG), kinase agents, MAPK, PI3K, and hypoxia-inducible factor inhibitors.¹⁸

The hypervascularity posing a high risk of serious bleeding during resection and the unpredictable development of metastases,^{3,12,14} are also important prognostic factors.

Imaging Evaluation

Anatomically, cardiac tumors can be classified as either intracavitary, mural, or intrapericardial. Many intracavitary and mural tumors can be diagnosed using transthoracic echocardiography. However, intrapericardial tumors are not easily visualized on transthoracic echocardiography and require cross-sectional imaging such as MRI or MDCT to diagnose.^{20,21} Typically, cardiac paragangliomas are incidentally found in patients with nonspecific cardiopulmonary symptoms. Alternatively, the tumor may be found because of symptoms directly related to functionality, mass effect, or invasion of adjacent structures such as the coronary vasculature and airways. Both modalities, MDCT and MRI, help in the assessment of the degree of invasion and extension of the lesion. MIBG SPECT can also be used to localize paragangliomas as well as to determine the presence of metastases.

On MRI, paragangliomas are generally iso- to hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images when compared with heart musculature.²² Diffuse enhancement on postcontrast images is the rule. Prominent “flow voids” indicate enlarged draining veins. T1 and T2 hypointensity foci with blooming on gradient echo images are explained by intralesional hemorrhage. More than 90% of paragangliomas will show positive radioiodine MIBG scan. Less commonly they will uptake the tracer on octreotide scans due to the presence of somatostatin receptors.

Differential Diagnosis on Imaging

Hypervascular mediastinal masses are rare. Vascular malformations, especially hemangiomas, may have an appearance similar to paragangliomas given the high vascularity and are usually recognized by the typical phleboliths and vascular channels.¹⁹ Giant lymph node hyperplasia (Castleman's disease) occurs in the mediastinum in 70% of cases. In particular, the hyaline unicentric form may present as an asymptomatic hypervascular mass similar to a paraganglioma.²³ Metastases from melanoma, renal cell carcinoma,

sarcoma, and lung and breast carcinoma are frequently hypervascular and heterogeneous, however, usually more than one lesion is present. In young patients, inflammatory pseudotumors may manifest as hypervascular lesions but rarely occupy the middle mediastinum.²⁴

Conclusion

Intrapericardial paragangliomas are located around the roots of the great vessels and atrioventricular groove where chromaffin cells are typically present. Encasement and wrapping of these structures seem to be a common feature with medium and large size tumors, a configuration that is not typical of other hypervascular lesions. Likewise, markedly avid IV contrast enhancement was reproducible in all patients. With medium and large tumors, a significant heterogeneous appearance was demonstrated. The presence of serpiginous structures surrounding the tumors was seen in nearly all cases in this series indicating the hypervascular nature.

When at least two of these three elements mentioned above are observed, the possibility of a paraganglioma should be strongly suggested in the differential diagnosis of a hypervascular mass, despite the rare occurrence. Pericardial effusions seem to be interestingly absent despite the tumor location. Laboratory/genetic tests and potentially additional imaging and may help shorten the time to diagnosis, which may be critical for a positive outcome after treatment. The detailed description of the tumor features is also a valuable indicator of the potential biopsy and surgical risk approach.

Conflict of Interest

None declared.

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