

## Cardiac Paraganglioma, Recent Advances in Clinicopathologic Features

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Cardiac paragangliomas (PGs) are rare neuroendocrine tumors comprising less than 1% of cardiac tumors. Few cardiac PG case reports and series are described in the literature. Cardiac PGs may be sporadic or arise from a syndromic association. Clinical presentations vary depending on the biochemical activity and location of the tumor. The left atrium, the right atrium, AP window, left ventricle, and atrioventricular groove are the most common sites for cardiac PGs, respectively. Many cardiac PGs are associated with succinate dehydrogenase (SDH) gene mutations. SDH-mutated PGs have aggressive histologic and clinical behavior. Therefore, PG patients should be screened for SDH mutations and provided with appropriate genetic counseling. SDH immunostaining can be used as a substitute diagnostic modality for SDH gene mutation and negative staining is associated with SDH mutation. Biochemical analysis, anatomical imaging, and functional imaging are also used for diagnostic workup of the tumor. Surgery is the only curative treatment for this tumor. Adrenoceptor blockers should be administered in functional PGs. PGs are highly vascular and frequently situated close to vital vessels. Accordingly, surgical complications such as bleeding are a leading cause of mortality in PGs. Metastatic PGs are only seen in a small subset of patients and are associated with poor clinical outcomes. Herein, we summarize clinical and pathological advances in cardiac PGs.

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## INTRODUCTION

Paragangliomas (PGs) are rare neuroendocrine tumors with an annual incidence rate of 1 per 300 000 individuals. PGs arise from neuroendocrine chromaffin cells presented in sympathetic and parasympathetic paraganglia. Sympathetic PGs commonly arise from abdominal sympathetic paraganglia. Sympathetic PGs are functional tumors that synthesize and secrete active metabolites (mainly norepinephrine and epinephrine).

Parasympathetic PGs are non-functional tumors and are commonly developed in the head and neck regions. Primary cardiac PGs are rare tumors accounting for less than 1% of all cardiac tumors and less than 0.3% of mediastinal tumors. These tumors may be either non-functional or functional; secreting catecholamines. The left atrium and aortic body are common sites for these tumors, but cardiac PGs have been reported in other parts of the heart.

The reason for this high site-specific occurrence is related to the presence of visceral paraganglia in the left atrium and branchiomeric autonomic paraganglia in the aortic body. Herein, we provide a comprehensive review of recent advances in clinical, genetic, pathological, diagnostic, and treatment aspects of cardiac PG.

### **Clinical Presentation**

The average age at diagnosis ranged from 42 to 52 years [1, 2]. PGs are slightly more common in females with male to female ratio of 0.85:1 [3]. Clinical presentation varies depending on the local effects and biological activity of the tumor. The most common symptoms in patients with cardiac PGs are often related to norepinephrine secretion [3]. These symptoms include hypertension, sweating, diaphoresis, palpitations, headache, and dizziness. Symptoms related to local tumor effects depend on the size and anatomical location of the tumor. These include heart failure, mitral insufficiency, embolization, and ischemic heart disease-like symptoms [4]. Constitutional symptoms not related to secretory profiles or local effects include weight loss, fatigue, and fever [3]. Some patients with cardiac PGs are asymptomatic and incidentally discovered by imaging.

### **The Genetic Basis of Paraganglioma**

Approximately 17 genes account for one-third of inherited PGs. Some of these genes are associated with the following inherited syndromes: familial PG syndromes, neurofibromatosis type 1, von Hippel–Lindau syndrome, and multiple endocrine neoplasia type 2 [5, 6]. Familial PG syndromes are commonly caused by germline mutations in succinate dehydrogenase (SDH) and succinate dehydrogenase complex assembly factor 2 (SDHAF2) genes [7, 8]. The SDH complex is located in the mitochondria (inner mitochondrial membrane) and contributes to energy production during the Krebs cycle through oxidation of succinate to fumarate. SDH is part of an enzyme complex with four subunits; performing different functions (two hydrophilic catalytic subunits, and two hydrophobic subunits). SDH subunit A (SDHA) is a flavoprotein that acts as a substrate-binding site for succinate. SDH subunit B (SDHB) is an iron-sulfur protein that, together with SDHA, forms the catalytic site of the enzyme. This

site oxidates succinate to fumarate. SDH subunits C and D (SDHC and SDHD) are located in the inner mitochondrial membrane, serve as membrane-anchoring subunits of the enzyme complex, play a part in electron transport and form the ubiquinone binding site [7-9]. Four assembly factors play a role in SDH complex assembly and maturation: SDH assembly factor 1 (SDHAF1), SDHAF2, SDHAF3, and SDHAF4 [9, 10].

Mutations in SDHA, SDHB, SDHC, SDHD, and SDHAF2 tumor suppressor genes account for 10%-30% of PGs/pheochromocytoma cases [10, 11]. Following the loss of heterozygosity and inheriting a germline mutation, the cell loses its normal functional allele and tumor formation occurs. Loss of a protein subunit results in destabilization of the SDH complex; leading to loss of its enzymatic activity [8]. These genes show an autosomal dominant pattern of inheritance with incomplete penetrance. In addition, SDHD and SDHAF2 mutations are maternal imprinted, meaning that the neoplasm will develop if the mutated gene is inherited from the father. Considering the individual skipping within a family as a consequence of incomplete penetrance and imprinting, family history is an ineffective tool for germline mutation screenings [12]. Therefore, genetic counseling and testing are recommended for all patients with PGs. PGs with SDH mutations are presented with aggressive features such as multifocal disease, the occurrence at a young age, and typically active metabolite secretion [7, 13-15]. Screening all PG patients for SDH mutations is essential. Genetic testing for SDH mutations is not available in all institutions and may be expensive with complicating comprehensive testing. Immunostaining for the surrogate marker of SDHB is an inexpensive and widely available SDH mutation screening tool [16-18]. Negative immunostaining for SDHB strongly suggests SDH mutation. Cardiac PGs are commonly associated with SDHB, SDHC, and SDHD genes. In one case series, 76.9% of tested patients with cardiac PGs had an underlying SDH mutation [1]. The high SDH mutation rate in cardiac PGs may be related to increased SDH mutations in extra-adrenal PGs [19]. Negative SDHB immunostaining is seen in ~40% of patients with cardiac PGs. We have previously demonstrated that SDHB-negative cases are correlated with aggressive histologic features [2].

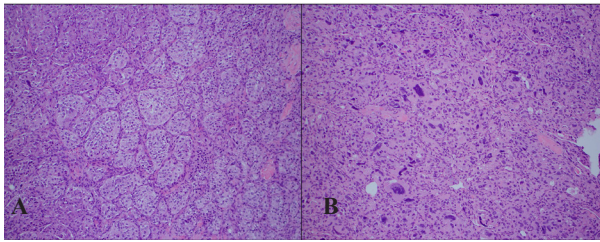
## Diagnosis

Initial clinical workup is dependent on the patient's presenting signs and symptoms. Functional PGs can be evaluated; using biochemical assays that measure plasma and/or urinary catecholamines and their metabolites (metanephrines). Indeed, most cardiac PGs are associated with elevated catecholamine [1]. Therefore, screening catecholamine secretion is a useful step to determine if the cardiac tumor is of chromaffin cell origin. Because PGs episodically release catecholamines, the sensitivity of catecholamine metabolites is relatively high [20]. Measuring plasma-free metanephrines can reach a sensitivity of up to 99% and specificity of up to 89%; while 24 hours urinary fractionated metanephrines sensitivity can reach 97%; however, the specificity is low (69%) [21]. A 2-fold increase in metanephrine levels above the upper limit is highly suggestive of PGs. However, small PGs and SDH-mutated PGs may not reach this threshold due to their lower catecholamine contents [22]. Although tissue biopsy is essential for the diagnosis, performing biopsy for the initial work-up is difficult and can result in bleeding complications due to the tumor's rich vascularity. Therefore, the biopsy is not recommended for the initial diagnostic work-up. Imaging studies have improved over the last few decades and have become very sensitive and specific for diagnosing and localizing cardiac PGs. Commonly used modalities include contrast-enhanced computed tomography (CT) scan, dedicated cardiac magnetic resonance imaging (MRI), transthoracic echocardiogram (TTE), and coronary arteriography [23]. By echocardiography, cardiac PGs appear as large, echogenic masses [4]. CT scan will show heterogeneous mass with peripheral enhancement and low attenuation areas due to tumor degeneration and necrosis [24]. By MRI, cardiac PGs are shown as well-circumscribed ovoid masses with hyperintense signals on the T2 imaging sequence [23]. Cardiac MRI is superior to CT scan and echocardiography for detection and evaluation of cardiac PGs [1]. In coronary arteriography, the tumor shows extensive parasitic vessels arising from the coronary arteries which are highly characteristic of PGs. This typical feature is different from typical myxomas or sarcomas [25]. Functional imaging studies can assist in the initial localization of the tumor and detection of metastasis.

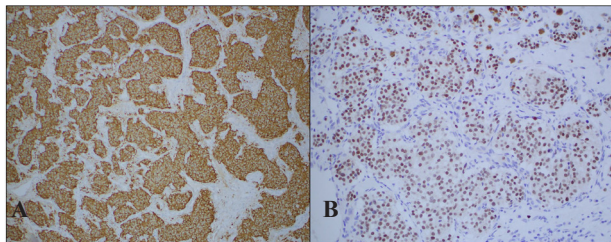
There are different radiopharmaceutical agents used to target different mechanisms of tumorigenesis in PGs. Iodine-123 metaiodobenzylguanidine (123I-MIBG) scan is one of the first modalities used for the diagnostic work-up for extra-adrenal PGs. The test has a sensitivity of 87% and a specificity of 100% [26]. However, the test has lower sensitivity when performed in patients with SDH genetic mutation [27]. 18F-fluorodeoxyglucose (18F-FDG) is another agent used with a sensitivity reaching 100% [1]. 68Ga-DOTATATE PET/CT scan is reported to have better sensitivity both in patients with germline SDH mutations and metastatic lesions [28]. Therefore, it should be the modality of choice in patients with cardiac PGs due to the high rate of SDH mutation.

## Pathology

The mean diameter of PGs is 5.3 cm (ranging from 1.5 to 15 cm) [3]. The most common sites of occurrence include the left atrium, followed by the right atrium, AP window, left ventricle, atrioventricular groove, interatrial septum, and right ventricle [26]. Approximately two-thirds of cardiac PGs are pericardial, and one-third is intracardiac. Grossly, these tumors are rubbery, round to oval, and encapsulated. The cut surface usually shows homogeneous pink-gray glistening parenchyma with no hemorrhage or necrosis [23, 29]. Histological examination is essential for differentiating PGs from other primary cardiac tumors, including myxoma, lipoma, rhabdomyoma, rhabdomyosarcoma, fibroma, hemangioma, angiosarcoma, papillary fibroblastoma, and leiomyosarcoma. The histologic features of cardiac PGs are similar to adrenal pheochromocytoma and PGs located in other areas. The tumor form well-defined nests of cuboidal cells (called Zellballen pattern) are separated by highly vascularized fibrous septa (Figure 1). The nests are surrounded by sustentacular cells. Each cell has a moderately abundant granular basophilic cytoplasm. The stroma is variable and may be very abundant and often with hyalinization. Mitotic figures are usually sparse. Atypical features such as bizarre nuclei, necrosis, increase mitosis, and vascular invasion are sometimes seen (Figure 2). However, none of these features should be taken as evidence of malignancy. Therefore, the terms "benign" or "malignant" PG should be avoided in the diagnosis [30].



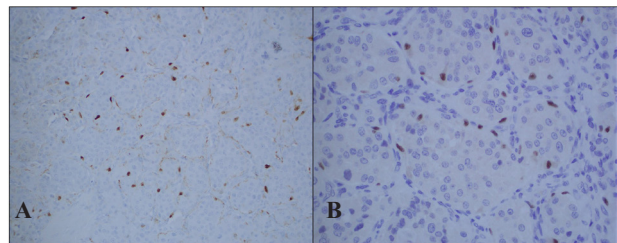
**Figure 1:** Histologic Features of Paraganglioma  
A) Classic cardiac paraganglioma shows a nested Zellballen pattern of tumor cells surrounded by sustentacular cells (Original magnification×100); B) A case of cardiac paraganglioma with atypical features such as variable cell sizes, nuclear enlargement, and pleomorphism (Original magnification×100).



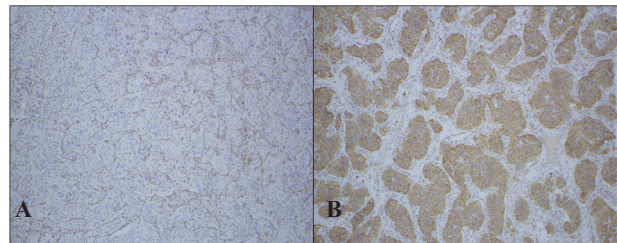
**Figure 2:** Immunohistochemical Stain Findings of Paraganglioma  
A) Synaptophysin which shows a granular cytoplasmic pattern (Original magnification×100); B) GATA3 which shows nuclear staining (Original magnification×200).

Immunohistochemically, PG cells are positive for chromogranin and synaptophysin (strong and diffuse cytoplasmic markers) (Figure 3A), and GATA3 (nuclear marker) (Figure 3B). The sustentacular cells surrounding the nest are positive for S100 and SOX10 (Figure 4A and 4B) and negative for synaptophysin and chromogranin. Ki-67 usually shows a low proliferation index (1-5%) [2]. Tumor cells are negative for melanocytic markers, cytokeratins, CD45, CD99, desmin, smooth muscle actin, and CD34 [23]. Immunostaining for SDHB is used as an initial screening for SDH family mutations, as tumors with SDH mutations will result in loss of the SDHB protein [16, 31]. Complete negative staining is strongly associated with SDH mutation; while positive staining indicates non-mutated SDH. Interpretation should be performed cautiously before reporting the result by assessing the pattern of staining in control samples. Internal positive control in endothelial cells, inflammatory cells, or stromal cells should be present before interpretation of the staining. A complete absence of SDHB immunostaining in neoplastic cells with no

positive internal controls should not be interpreted. The staining pattern for SDHB immunostaining can be divided into complete absent staining, weak bluish cytoplasmic staining, and distinct granular cytoplasmic staining. Complete absent staining and weak bluish cytoplasmic staining are characteristics of a negative result, while distinct granular staining is a normal staining pattern and is considered to be positive. A negative result with a complete absence of staining is correlated with SDHA, SDHB, or SDHC mutation, while weak bluish cytoplasmic staining is correlated with SDHD mutation [16].



**Figure 3:** Immunohistochemical Staining for the Sustentacular Cells Surrounding the Tumor Nests by S100 (A, Original magnification×200) and SOX10 (B, Original magnification×400)



**Figure 4:** Examples of Immunohistochemical Staining for SDHB  
A) SDHB-negative case showing the absence of staining in the tumor cells; B) Strong granular cytoplasmic staining in the tumor cells (Original magnification×100).

### Treatment

Surgery is the only curative option available for these tumors. Due to their location, surgical removal of cardiac PGs is difficult and may be accompanied by dangerous complications. Therefore, the assessment of myocardial and valvular function is mandatory. As most cardiac PGs produce catecholamines, preventing life-threatening complications, such as cardiac arrhythmias, hypertensive crisis, or myocardial infarction, is an important and critical part of treatment in these patients. Therefore, an important and critical part of treatment is the administration of  $\alpha$ -adrenoceptor

and  $\beta$ -adrenoceptor blockers at least two weeks before surgery [20]. Hence, an essential part of treatment is the use of  $\alpha$ -adrenergic blockers; starting two to three weeks before surgery. Also, starting  $\beta$ -blockers two days before surgery has been suggested for heart rate control. However, it should be kept in mind not to give a beta-blocker unless the alpha-blocker has successfully controlled the blood pressure. Otherwise, alpha-receptor stimulation could lead to a catecholamine storm and hypertensive crisis [22]. The first step before the surgical management of cardiac PGs is to determine whether the tumor is resectable or not. Therefore, pre-operative assessment should include the tumor's location, the proximity of the tumor to cardiac structures and great vessels, and its extracardiac extension [22]. The common approach for tumor resection is sternotomy with cardiopulmonary bypass followed by the right or left thoracotomy [3]. Superficial non-invasive tumors can be removed without cardiopulmonary bypass [23]. In cases with extensive cardiac invasion, resection may require grafting and reconstruction of the damaged structures. Difficult cases may also require complete removal of the heart and resection of the tumor followed by auto-transplantation [26]. Depending on the tumor's location and the complexity of the surgery, the mortality rate may reach 10-20% [26, 32]. The most common complication is hemorrhage which can be attributed to the high vascularity of these tumors. Other reported complications include sepsis and myocardial infarction. Treatments with chemotherapeutic agents and radiation therapy have been attempted especially for metastatic tumors; however, their effect remains uncertain [1, 3].

### Prognosis

Most cardiac PGs are benign tumors. After successful resection, patient survival rates are equal to age-matched individuals in the general population [23]. Metastatic PGs are associated with a marked decrease in the survival rate [1, 3]. Several grading systems including the Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) and Pheochromocytoma of the Adrenal Scaled Score (PASS) can be used to predict the metastatic potential of PGs [33]. PASS scoring system is based on multiple histological parameters; however, the system has inter- and intraobserver variability in

some of the histological features. GAPP eliminates some of the poorly concordant histological features and adds biochemical and Ki-67 immunostaining. Modified – GAPP improved the lack of SDHB immunostain. GAPP and modified- GAPP scoring systems have a better predictive value for high-risk PGs [33].

### CONCLUSION

In summary, cardiac PGs are uncommon tumors often located in the left atrium. Most cardiac PGs are functional and secrete catecholamines, leading to various symptoms including hypertension, sweating, diaphoresis, palpitations, headache, and dizziness. Therefore, for initial screening, biochemical analysis is useful and precedes anatomical (by CT and MRI) and functional imaging. Histologically, PGs are characterized by well-defined nests surrounded by sustentacular cells that are separated by highly vascularized fibrous septa. SDH mutations in PGs can be germline or sporadic and are associated with aggressive disease. Therefore, screening patients with PGs for SDH mutations may help to stratify the risk of metastasis. Inherited cases may benefit from genetic counseling. Finally, SDHB immunostaining is recommended as a screening tool that can help to screen patients with possible SDH mutation.

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### CONFLICT OF INTEREST

The authors declared no conflict of interest.

### ETHICS APPROVAL

Ethical approval is not required for this review article.

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