

Surgical Treatment of Primary Cardiac Paragangliomas: A Single-Center Experience

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ABSTRACT

Background: Cardiac paragangliomas are rare neuroendocrine tumors that will cause significant morbidity if left undiagnosed. Because of the paucity of cohort data, their rapid diagnosis and appropriate management still pose unique challenges to cardiac surgeons. We aimed to investigate the clinical features and surgical management of primary cardiac paragangliomas in our single center.

Methods: From May 2014 to October 2020, patients diagnosed with primary cardiac paragangliomas retrospectively were reviewed. Demographic data, clinical presentation, preoperative imaging methods, surgical resection, perioperative management, histological analysis, and outcomes were recorded. Postoperative follow up also was reviewed.

Results: With multiple imaging methods, including echocardiography, computed tomography, positron-emission tomographic-computed tomography, and biochemical tests, there were five cases of primary cardiac paraganglioma verified by postoperative immunohistochemical staining, two of which were hormonally active. There were no metastatic cardiac paragangliomas, according to positron-emission tomographic-computed tomography, and all patients accepted surgical treatment. Preoperative adrenoceptor blockade was given to hormonally active patients, accordingly. Complete resection of the tumor was accomplished under cardiopulmonary bypass in each case. Tumor distribution included two masses on the roof of the left atrium, two masses in the right atrioventricular groove, and one between the ascending aorta and main pulmonary artery. Immunohistochemical staining for chromogranin, neuron-specific enolase, synaptophysin, and S-100 were positive, which were typical of cardiac paraganglioma. There were no operative deaths. All the patients had an uneventful recovery except one patient who underwent low cardiac output syndrome. During follow up (mean 4.2 years, range 0.6-7.0 years), all patients were well with New York Heart Association class I or II. Only one patient developed thyroid carcinoma three years after surgery but with no paraganglioma recurrence

during periodic computed tomography, and this patient recovered well after thyroidectomy.

Conclusion: Although cardiac paragangliomas are rare and may present surgical challenges for clinicians, surgical resection remains the choice of treatment with favorable outcomes through a multidisciplinary heart team. Moreover, lifelong surveillance still is recommended to detect possible recurrence or associated nonchromaffin tumors in time.

INTRODUCTION

Paragangliomas are one kind of extra-adrenal neuroendocrine tumor that arise from chromaffin cells of the sympathetic gang. Cardiac paraganglioma is extremely rare, accounting for less than 1% of primary cardiac tumors and less than 0.3% of mediastinal tumors [Lenders 2014; Yanagawa 2018]. Some cardiac paragangliomas are of the sympathetic nervous system and may present with symptoms of catecholamine excess, such as severe hypertension; some of them are of the parasympathetic nervous system and usually nonfunctional and incidentally diagnosed [Lam 2017]. Because of its low incidence, challenges still exist, regarding its rapid diagnosis and management. In the present study, five patients with primary cardiac paraganglioma in our center received surgical treatment from May 2014 to October 2020. The clinical manifestations, pathological characteristics, and surgical results were reviewed.

METHODS

Preoperative clinical data: Five patients (three males and two females; mean age 51.5 years, range 35-59 years) were reviewed in this study. Main symptoms included dyspnea on exertion and fatigue in two patients, paroxysmal hypertension in two patients, and asymptomatic in one patient. There was no obvious family history for these patients. Urinary norepinephrine was elevated in two patients with hypertension in a 24-hour urine catecholamine assay, and the two patients were placed on α -adrenoceptor and β -adrenoceptor blockers prior to surgery.

Preoperative imaging methods, including echocardiography, contrast-enhanced computed tomography (CT)/coronary computed tomographic angiography (CTA), and whole-body ^{18}F -fluoro-2-deoxy-glucose (^{18}F -FDG) positron-emission tomographic-computed tomography (PET-CT),

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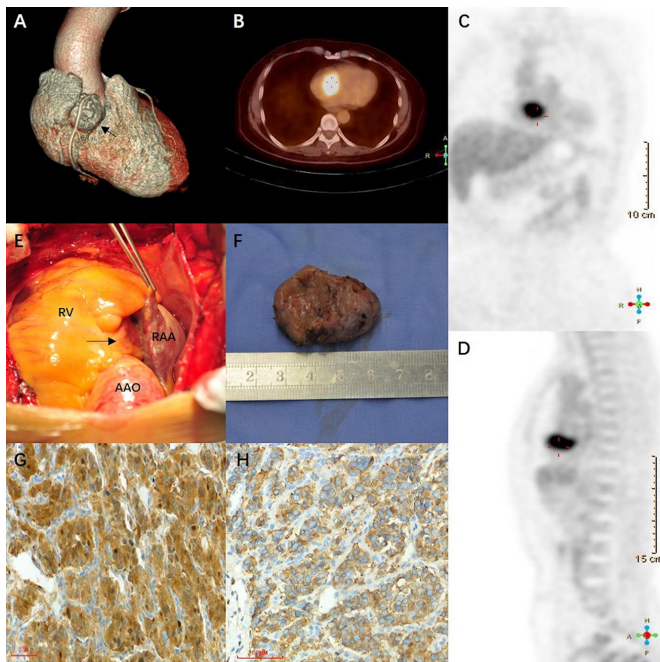


Figure 1. A representative case of cardiac paraganglioma. A) A 4.9×3.1×2.6-cm tumor in the right atrioventricular groove (arrow) seen in 3D reconstruction on coronary CTA. B, C, and D) A similar-sized FDG-avid soft tissue mass (maximum standardized uptake value 9.6-11.6) at the same location as coronary CTA indicated seen on whole-body 18F-FDG-PET-CT with no metastasis. E and F) Intraoperative inspection of the mass and the excised specimen. G and H) These panels, respectively, show neuron-specific enolase staining and S-100 staining.

were used to locate the mass and evaluate the key features of the mass (Figure 1A-1D). Multiple imaging techniques showed that two masses were located on the roof of left atrium, two masses in the right atrioventricular groove, and one between the ascending aorta and main pulmonary artery.

Intraoperative myocardial preservation and surgical treatment: After general anesthesia, transesophageal echocardiography (TEE) routinely was adopted to confirm the masses and evaluate heart function. Surgeries were performed through median sternotomy with the help of cardiopulmonary bypass (CPB). During surgery, the heart was arrested with antegrade modified Del Nido cardioplegia. After careful inspection, all the masses successfully were resected (Figure 1E-1F), and the defects after resection were reconstructed with an autologous pericardial patch, if necessary. The mean arterial blood pressure during CPB was maintained between 50 to 70 mmHg. After weaning from CPB, proper arterial blood pressure was maintained to prevent hypertensive crisis or severe hypotension. After completion of surgery, TEE again was used to evaluate ejection fraction and if residual mass still existed. Mean duration of CPB was 128 minutes (range 113-149 minutes). Mean duration of aortic cross-clamping was 65 minutes (range 58-73 minutes).

The excised masses were confirmed histologically and by immunohistochemistry to be paragangliomas. Hematoxylin and eosin staining showed uniform cells with fine stippled

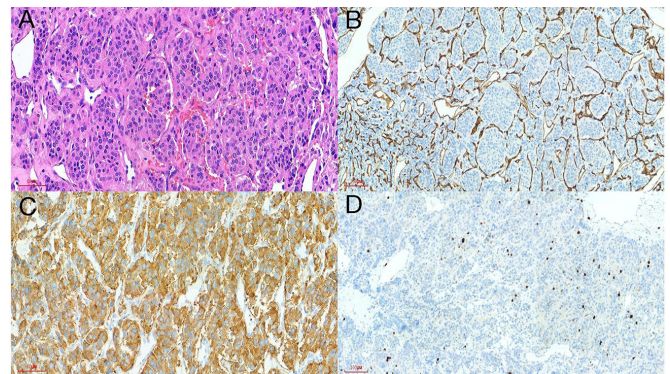


Figure 2. Hematoxylin and eosin and immunohistochemical staining. A) Hematoxylin and eosin staining. B) CD34 immunostaining. C) Synaptophysin immunostaining. D) Ki67 staining.

chromatin pattern and pale eosinophilic cytoplasm arranged in trabecular and organoid growth, which is typical of paraganglioma (Figure 2A). Neuron-specific enolase (Figure 1G) and synaptophysin staining (Figure 2C) were positive, indicating neuroendocrine origin (Figure 3). Surrounding supporting sustentacular cells were highlighted by S-100 immunostaining (Figure 1H). CD34 immunostaining showed a delicate vascular framework separating tumor nests (Figure 2B). The Ki67 staining showed a low proliferation index (Figure 2D).

RESULTS

There were no in-hospital deaths or severe complications, such as unplanned reexploration for bleeding, vasoplegia, or hypertensive crisis. Mean mechanical ventilation time was 9.6 hours (range 7.5-11.7 hours). Average ICU length of stay was 2.5 days (range 2-5 days). Postoperative echocardiography showed normal ejection fraction except one with low cardiac output syndrome, which was successfully treated by inotropes. There were no residual tumors left on echocardiography. Also, 24-hour urinate catecholamine level was normal after surgery.

Mean follow up was 4.2 years (range 0.6-7.0 years). During follow-up surveillance, only one patient was diagnosed with thyroid carcinoma but with no paraganglioma recurrence during periodic CT imaging and recovered well after sub-total thyroidectomy.

DISCUSSION

Clinical features and diagnosis

Cardiac paragangliomas are a subset of paragangliomas. Because of their extremely low incidence and a broad spectrum of presenting symptoms, rapid diagnosis sometimes may be challenging for clinicians. Based on the secretory profile of catecholamines, cardiac paragangliomas largely are categorized into two types: hormonally active type and hormonally inactive type. Headaches, palpitations, and sweating

are typical symptoms of hormonally active cardiac paragangliomas caused by excessive release of catecholamines [Brown 2008]. For hormonally inactive type, patients may present non-specific symptoms due to localized mechanical compression of a cardiac chamber or obstruction to normal blood flow within the cardiac chamber [Huo 2012]. These patients are clinically less common than hormonally inactive type patients. In our series, only one patient was asymptomatic who was incidentally diagnosed. Most of the patients (four out of five patients) were symptomatic because of catecholamine excess, which is similar to the result of one meta-analysis of cardiac paragangliomas [Wang 2015].

Biochemical testing routinely was performed to confirm the excessive release of catecholamines, if cardiac paragangliomas were suspected. According to the available literature, plasma metanephrine testing (sensitivity 96%, specificity 85%) and 24-hour urinary catecholamines (sensitivity 88%, specificity of 99.7%) are mainly two screening tests [Lenders 2002]. In this review, we used a 24-hour urine catecholamine assay to assist diagnosis of functional cardiac paragangliomas and postoperative surveillance. Two patients had elevated values which were >2 times the upper limit of the normal range, and all patients had normal values after surgical resection during postoperative surveillance.

Other than clinical presentation and biochemical proof of excessive release of catecholamines, anatomical imaging of the tumor also is required to diagnose cardiac paragangliomas. Multiple imaging modalities, including echocardiography, contrast-enhanced CT, and cardiac magnetic resonance imaging (MRI), may be considered in the anatomical localization of the tumor and evaluation of the key characteristic features of the tumor required for surgical planning. Transthoracic or transesophageal echocardiography routinely is used as the initial test because of its ease of availability and good diagnostic sensitivity [Meng 2002]. Contrast-enhanced CT has a higher resolution than echocardiography and can provide detailed information about possible blood supply for the tumor from the coronary artery. Although MRI has a higher temporal and spatial resolution, it is a lengthy test, relatively expensive, and may not be universally available.

Besides anatomical imaging, functional imaging is also indicated to rule out metastasis of the tumor and multifocality, which will guide the final decision on proceeding with surgery or systemic therapy. According to the literature, total-body nuclear scan with ¹²³I-labeled metaiodobenzylguanidine (MIBG) or PET-CT with ⁶⁸Galabeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-octreotate (DOTATATE) or ¹⁸F-FDG is preferred to search for additional paragangliomas or possible metastatic disease [Han 2019]. Although there are many different imaging options mentioned above, the exact selection should be individualized, according to different clinical scenarios and availability in each center. Our approach to diagnosis often includes urine catecholamine assay, transthoracic and intraoperative transesophageal echocardiography, contrast-enhanced CT combined with ¹⁸F-FDG-PET-CT for differentiation between cardiac paragangliomas and other primary cardiac tumors.

Surgical treatment and perioperative management

About 10% of the paragangliomas could be malignant, so most patients prefer to select surgical therapy to avoid the risk of undiagnosed malignancy [Vander 2000]. So now, surgical resection remains the cornerstone of cardiac paraganglioma therapy [Plouin 2001]. The timing of surgery and surgical approach are two major concerns. For hormonally active patients, preoperative adrenoceptor blockade treatment was conducted as recommended by the Endocrine Society practice guidelines to control blood pressure and prevent intraoperative hypertensive crises [Chen 2010]. For hormonally inactive patients up to now, there are no clear guidelines on preoperative management. So, we just put two patients with hypertension on adrenoceptor blockers but not for other patients. The surgical approach for cardiac paragangliomas now is mainly via median sternotomy with the help of CPB to completely resect the tumor and possibly infiltrated cardiac tissues and also allow for easy concomitant patch reconstruction of the defect. Resection without CPB also was possible, if the location of the tumor was easy to expose with no hemorrhage risk [Yadav 2014]. In our series, all tumors were resected completely under CPB with two masses on the roof of left atrium, two masses in the right atrioventricular groove, and one between the ascending aorta and main pulmonary artery as preoperative imaging indicated. With meticulous maneuvers and good protection of coronary arteries, no serious concomitant surgeries, such as coronary artery bypass grafting, were warranted.

Postoperative management should be focused on avoiding perioperative hemorrhage and sustained hypotension, which usually could be treated with inotropic agents and vasopressors. Very rarely is ECMO necessitated because of vasoplegia [Liu 2019]. We tried to prevent hemorrhage complications by careful intraoperative treatment of blood supply branches from coronary artery and meticulous hemostasis after protamine administration.

Follow-up surveillance

For patients with benign paraganglioma, survival following surgical resection is similar to that of the age-matched normal population. However, for patients with metastatic paraganglioma, 5-year survival is <50% of age-matched controls [Bravo 2003]. Although recurrence is rare for benign paragangliomas after surgery, lifelong surveillance still is recommended, especially for metastatic disease. It is reported that the mean incidence of recurrence could be as high as 15% after five years and 23% after 10 years for abdominal extra-adrenal paragangliomas [Van Slycke 2009]. After surgical resection, annual biochemical testing for ≥10 years is recommended for hormonally active cardiac paragangliomas and periodic imaging for hormonally inactive cardiac paragangliomas [Erickson 2001; Hardegree 2012]. During postoperative periodic CT imaging, only one patient was diagnosed with associated non-chromaffin tumor-medullary thyroid carcinoma three years after primary cardiac paraganglioma surgical resection and recovered well after sub-total thyroidectomy.

Limitations

Our study is a single-center review and limited by the relatively small number of patients because of its inherited

extreme low incidence. What's more, being not as readily available, genetic testing for susceptibility genes, such as succinate dehydrogenase genes, was not performed for previous cases, which otherwise would provide more detailed features for clinical management strategies.

CONCLUSION

Cardiac paragangliomas are exceptionally rare neuroendocrine tumors, and clinicians should be vigilant not to misdiagnose them. Early surgical resection without intraoperative rupture of the tumor capsule should be the treatment of choice to avoid the risks of lethal paroxysm and metastatic disease. With the help of a multidisciplinary heart team, good postoperative survival, and long-term outcomes can be ensured through an organized care program. However, because of the potential of recurrence, lifelong surveillance is recommended.

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