



Case Report

Primary unresectable locally invasive biatrial paraganglioma presenting with chest pain



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ABSTRACT

Paragangliomas, neuroendocrine tumors of neural crest origin, commonly occur in the adrenal medulla where they are called pheochromocytoma. Primary cardiac paragangliomas are uncommon whereby they arise in the left atrium and, less frequently, right atrium. We present a 43-year-old female with a cardiac paraganglioma presenting with ischemic and positional chest pains. CT scanning showed an infiltrative 15 × 10 cm unresectable tumor with intense peripheral enhancement and central hypoattenuation located above the right atrium. The clinical impression was that of a high-grade sarcoma. Histopathological examination revealed tumor cell nests in a distinctive ‘Zellballen’ pattern with positive synaptophysin, chromogranin and GATA-3 staining confirming the diagnosis of paraganglioma. Immunohistochemical studies revealed that the tumor lacked the expression of *SDHB* and therefore indicating a *SDHB* gene mutation. The tumor was nonfunctioning, and therefore the absence of the classic adrenergic manifestations contributed to the late diagnosis of the condition. In conclusion, whereas preoperative diagnosis is challenging with nonfunctional paragangliomas, it is recommended that paragangliomas be considered in the differential diagnosis of cardiac neoplasms.

1. Materials and methods

A 43-year-old woman with unremarkable past medical history presented with a recent onset of exertional dyspnea, positional chest pressure and sinus tachycardia. There were no symptoms or signs indicating increased catecholamines release such as diaphoresis, anxiety, hypertension or hyperglycemia. Chest radiograph showed a lobulated mass situated above the right atrium. Chest CT scan demonstrated a 10 × 15 cm mediastinal mass with intense, thick nodular peripheral enhancement and central hypoattenuation in addition to associated mass effect on adjacent structures including the aorta and the left atrium (Fig. 1). Echocardiography revealed normal regional wall motion, normal right ventricular cavity size and systolic function, normal left atrium cavity size and no pericardial effusion. Transesophageal echocardiogram revealed the involvement of the right atrium, the roof of the left atrium and the septum, with the tumor mass circumferentially surrounding the superior vena cava. Because the patient was not a candidate for heart transplantation or ventricular assist device, right atrium reconstruction with bovine patch was performed following the tumor excision.

Grossly, the tumor appeared as a globular firm rubbery tan/gray mass. Microscopic examination revealed monomorphic tumor cell nests

with fine salt-and-pepper chromatin arranged in a distinctive ‘Zellballen’ pattern and separated by reticulin fibers; a pattern suggestive of paraganglioma (Fig. 2A and B). The immunohistochemical profile of the tumor showed strong positive staining of the tumor cells with synaptophysin, chromogranin and GATA-3 (Fig. 2C, D and E), negative staining with cytokeratin marker AE1/3 and SDHB (Fig. 2G and H), and weak staining of the sustentacular cells with S-100. The endothelial marker CD34 highlighted the intratumoral blood vessels (Fig. 2F). The immunophenotype confirms the diagnosis of paraganglioma with *SDHB* mutation.

2. Discussion

Paragangliomas are rare extra-adrenal tumors of neuroectodermal origin that arise from chromaffin cells of the sympathetic ganglia. Morphologically and immunohistochemically, paragangliomas resemble pheochromocytomas arising from the adrenal medulla. Paragangliomas are divided into those that derive from the sympathetic paraganglia versus those from parasympathetic paraganglia which tend to be hormonally inactive, less likely to be malignant and may be correlated with living at high altitude [1]. The incidence of paragangliomas is 10% that of pheochromocytomas, which is equivalent to

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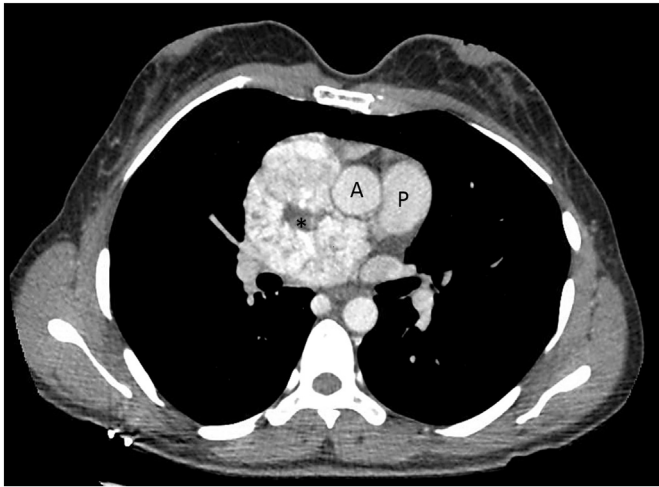


Fig. 1. shows a CT scan picture of the chest showing a nodular tumor, hyperattenuating and peripherally enhancing with central hypoattenuation (asterisk). No invasion, albeit mild compression, of the aorta (A) or pulmonary artery/trunk (P) is seen.

approximately 0.01–0.001% of the general population [2]. Cardiac paragangliomas are exceptionally rare amounting to 1–2% of all paragangliomas [3], with only few reported cases [3–12]. The differential diagnosis of cardiac tumors includes benign tumors (75%) such as myxomas being the most frequent, lipoma and lipomatous hypertrophy, valvular fibroelastic papilloma, fibroma, hamartoma, rhabdomyoma and paraganglioma. The malignant tumors amount to only 25% of cardiac tumors and include sarcomas, lymphomas and pericardial mesothelioma [13]. Ten percent of paragangliomas are malignant as evidenced by distant metastasis. Misdiagnosis of the tumor as a myxoma reportedly lead to post-operative mortality possibly from catecholamine release precipitated by surgical handling [9].

A retrospective study reports that in 12 cardiac paragangliomas cases, the tumor size ranged from 3 to 8 cm and the median patient age to be 35 [2]. Tumor degeneration and/or necrosis was seen in 50% of cases and calcification was a rare observation. The most frequent cardiac location of paragangliomas was the left atrium (83%), with 50% of the tumors showing evidence of myocardial invasion. A larger-scale study reports the left atrium to be the most frequent site (38.5%) besides other cardiac locations including the right atrium (19.2%), aortic-pulmonary window (18%), left ventricle (7.7%), atrioventricular groove (6.4%), inter-atrial septum (5.1%) and right ventricle (4%) [10]. In our case, the tumor was a 15 × 10 cm mass which involved both the right and left atria.

Most (79%) paragangliomas are catecholamine-secreting tumors [10] presenting with adrenergic manifestations such as palpitation, diaphoresis, hypertension and anxiety. Alternatively, some patients present with clinical picture of heart failure and hypotension due to altered atrial filling and the subsequent hemodynamic disturbance or from adrenergic cardiomyopathy [14]. Impinging on coronary arteries can potentially lead to ischemic manifestations such as acute myocardial infarction and stroke [12], whereas a number of the paragangliomas are incidentally diagnosed. Our case had a unique presentation with a mix of ischemic picture in the form of exertional pain and non-ischemic manifestation in the form of positional pain. Because of the endocrine activity, diagnosis can be made by detecting elevated plasma metanephrines with sensitivity and specificity of 99% and 89% or urine metanephrines with sensitivity and specificity of 97% and 93%, respectively. Measuring serum and urine total catecholamines is less reliable [15]. Imaging techniques like contrast CT scan, magnetic resonance imaging (MRI) and metaiodobenzylguanidine (MIBG) scan remain superior in detecting the tumor location and potential metastasis [2] with combined MRI and MIBG scan providing 100% sensitivity and positive predictive value [16].

Apart from the endocrine consequences of cardiac paragangliomas, certain surgical complications should be taken into account [4]. Hemorrhage, due to the rich vascularity of the tumor which tends to derive its blood supply from the coronaries, is the most common cause of perioperative mortality in such patients [10]. Furthermore, post-operative circulatory collapse can develop due to vascular volume depletion, vasoactive mediators released during extended cardiopulmonary bypass, lingering pre-operative α -adrenergic blockers or abrupt catecholamine withdrawal [11]. Ultimately, paragangliomas deeply invading the myocardium is a common complication in 64% of cases [10] which may necessitate considerable surgical reconstruction or cardiac transplantation [4,5,17]. Detailed perioperative anesthesiological and surgical considerations are described elsewhere [4,7,8,10,17].

The management requires controlling the excessive adrenergic effects through α and β adrenergic receptor blockers prior to the surgical excision of the tumor, with α blockade commenced weeks before β blockade to avoid hypertensive crises. Alternatively, calcium channel blockers and metyrosin, a competitive inhibitor of the rate-limiting enzyme in norepinephrine synthesis, can be used if α and β blockers are to no avail [8,17]. Ultimately, surgical excision remains the chiefly curative solution [4,10] with 10 year survival > 80% [8]. As far as the prognosis of cardiac paragangliomas is concerned, tumor size or endocrine activity, patient's age, the extent of cardiac reconstruction and different surgical techniques do not seem to correlate with mortality, while myocardial invasion showed a statistically insignificant trend towards increased mortality. Distant metastasis is the only factor that best correlates with long-term survival [10].

Certain germline mutations are associated with the development of pheochromocytoma and paraganglioma such as von Hippel–Lindau disease (*VHL* gene), neurofibromatosis 1 (*NFI* gene) and multiple endocrinal neoplasia type II (*RET* proto-oncogene) [1]. Familial paraganglioma shows autosomal dominant inheritance and is classified into types PGL1 through 5 based on the mutated mitochondrial succinate dehydrogenase (SDH) subtype (*SDHD*, *AF2*, *C*, *B* and *A*, respectively) [1]. In this regard, approximately 40% of all paragangliomas are associated with SDH deficiency, as opposed to only 3% of pheochromocytoma [18]. Immunohistochemical evaluation of SDHB is used to screen for the potentially hereditary cases in addition to risk stratification since *SDHB* mutations are strong predictors of both metastasis and poor outcome [19]. A study by the Pheochromocytoma Study Group in Japan (PHEO-J) suggested that a combination of the GAPP (grading system for adrenal pheochromocytoma and paraganglioma) and SDHB immunohistochemistry may be helpful to predict tumor with high metastatic potential [20]. A number of the recently published cardiac paraganglioma cases were associated with *SDHB* mutations (Table 1). Carney's triad is a combination of paraganglioma, pulmonary chondroma and gastrointestinal stromal tumor (somatic activating mutation of *cKIT*) [21], whereas Carney-Stratakis syndrome is a dyad of gastrointestinal stromal tumor and paraganglioma due a mutation of the succinate dehydrogenase-coding gene *SDHB*[22]. On the other hand, hereditary leiomyomatosis and renal cell cancer (HLRCC) is caused by mutations in fumarate hydratase [23]. Upon suspicion of inherited forms of paraganglioma, guidelines recommend the use of a clinical feature-driven diagnostic algorithm to guide specific genetic testing [1,24]. Regarding the sporadic genomic mutations associated with pheochromocytoma and paraganglioma, the TCGA study has reported a novel gene fusion (*MAML3*) that activates the Wnt signaling pathway associated with clinically aggressive disease and metastasis. Moreover, the study suggested that somatic mutations in the cold shock domain-containing E-1 gene (*CSDE1*) play a significant role in promoting neoplastic cell proliferation in pheochromocytoma and paraganglioma [25].

With respect to metastasis, histological features are not reliably used to predict metastatic diseases, and metastatic paraganglioma should only be suspected when tumor cells are found in unusual location for

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