



Delayed Paraganglioma Diagnosis: A Case Report and Literature Update

Şamil Ecirli¹, Mustafa Korkmaz¹, Orkide Kutlu², Cevdet Duran¹, Mustafa Önder Gören¹, Abdullah Sakin³

Abstract

Paragangliomas are rare catecholamine secreting neuroendocrine tumors arising from extra-adrenal autonomic ganglia. Almost all sympathetic paragangliomas secrete norepinephrine and present with hypertension, headache, sweating, and tachycardia episodes similar to pheochromocytoma. Parasympathetic paragangliomas of which localized along the glossopharyngeal/vagal nerve through the neck and skull base are usually nonfunctional 80%–90%, and create a clinic with mass effect. Herein, we report a patient who had hypertensive crisis and pulmonary edemas several times, diagnosed as paraganglioma.

Keywords: Paraganglioma, pheochromocytoma, extra-adrenal, cardiac arrest

Introduction

Paragangliomas are neuroendocrine tumors that arise from extra-adrenal autonomic ganglia; they are rarely encountered and can secrete catecholamines. Their incidence was reported between 0.01 and 0.1%. A higher incidence in autopsy series suggests that most of these tumors remain undiagnosed for a lifetime. Paragangliomas and pheochromocytomas are closely associated with each other; it is not possible for them to be distinguished at the cellular level. In the 2004 classification of endocrine tumors by the World Health Organization (WHO), pheochromocytomas were called as “intra-adrenal paragangliomas,” and some researchers termed sympathetic paragangliomas as “extra-adrenal pheochromocytomas.” However, in the general approach, pheochromocytomas are used for secreting tumors arising from the adrenal medulla, and regardless of catecholamine secretion, paragangliomas are used for tumors arising from paraganglions except for the adrenal gland. Parasympathetic paragangliomas are coincidentally found in radiological examinations or during scanning in known mutation carriers (1).

Herein, we report a patient with paraganglioma who was returned to life with resuscitation after cardiac arrest, hospitalized in the intensive care units due to hypertensive crisis and acute pulmonary edema several times, placed with implantable cardioverter defibrillator considering diagnosis of acute coronary syndrome, Brugada syndrome, and Takotsubo cardiomyopathy.

Case Report

A 37-year-old female patient underwent resuscitation in the center where she applied with complaints of headache for 10 months, nausea, vomiting, palpitation, and dyspnea. She was followed in reanimation and coronary intensive care units (CICUs) with the diagnosis of Brugada syndrome after resuscitation. The patient was discharged with the treatment of 100 mg of acetylsalicylic acid and 25 mg of metoprolol and was admitted to the cardiology service in a tertiary center due to palpitation, sweating, trembling, flushing, nausea, and severe headache attacks after approximately 1 month. An implantable cardioverter defibrillator was mounted on the patient who was brought to the council considering Takotsubo cardiomyopathy and was discharged after starting 5 mg of bisoprolol. The patient whose complaints started again approximately 7 months later was hospitalized with the diagnosis of acute hypertensive crisis and pulmonary edema twice at an epicenter CICU in the last 2 months. The patient was performed coronary angiography twice with no diagnosed lesions, applied to us. In the examination, the patient had an arterial blood pressure of 100/70 mmHg, pale appearance, venous fullness in the neck, hepatojugular reflux, tachycardia and grade 2/6 systolic murmur was heard. Hemoglobin levels were found to be 10.5 (normal 12–16) g/dL, ferritin was 6.9 (normal 14–150) ng/mL, and sedimentation was 72 (normal 0–25) mm/h. Electrocardiogram was normal, and the ICD view was obtained on telecardiography. The ejection fraction was found to be 60% on echocardiography. In ultrasonography (USG), a 6.5×4-cm mobile

This study was presented at the 36th Endocrinology and Metabolic Congress, 21-25 May 2014, Antalya, Türkiye.

¹Clinic of Internal Medicine, Okmeydanı Training and Research Hospital, Istanbul, Türkiye

²Clinic of Internal Medicine, Konya Training and Research Hospital, Konya, Türkiye

³Clinic of Medical Oncology, Okmeydanı Training and Research Hospital, Istanbul, Türkiye

Address for Correspondence:
Orkide Kutlu
E-mail: orkidekutlu@windowslive.com

Received:
28.07.2015

Accepted:
04.09.2015

© Copyright 2015 by Available online at
www.istanbulmedicaljournal.org

mass with a smooth contour showing cystic areas was observed in the lower pole of the right kidney, anterior neighborhood of the inferior vena cava. An increased vascularity was observed in the doppler examination. On abdominal computed tomography, a 42×60×65-mm heterogeneous solid mass with necrotic components in the right paraduodenal space, pressing duodenal loops toward anterior/inferior vena cava toward posterior was evaluated as a paraganglioma (Picture 1). In the 24-h urinary examination of the patient, 1365.8 (normal 23–105) mcg of norepinephrine, 45.7 (normal 4–20) mcg of epinephrine, 6695.2 (normal 0–390) mcg of normetanephrine, 1052.8 (normal 0–320) mcg of metanephrine, 247.3 (normal 190–450) mcg of dopamine, and 32.7 (normal 0–6.6) of vanilmandelic acid were detected. On positron emission tomography (PET), the metastasis was not detected. The patient was prepared for surgery with 2 mg of doxazosin, 5 mg of bisoprolol and hydration.

Discussion

Of all catecholamine-secreting tumors, 5–20% are extra-adrenal paragangliomas. They may be solitary/multiple, sporadic/hereditary, benign/malignant in various locations. Some hereditary paragangliomas, especially those originating from the head and neck, are associated with the mutation in the gene encoding different subunits of the succinate dehydrogenase (SDH) enzyme complex. However, pheochromocytomas/paragangliomas may be associated with multiple endocrine neoplasia 2A and 2B (MEN 2), neurofibromatosis type 1 (NF1), von Hippel–Lindau and Carney–Stratakis complex. Most hereditary paragangliomas are associated with SDHD, SDHB, SDHC, VHL, RET, and NF1 mutations. While multiple paragangliomas appear at a rate of 17–85% in hereditary cases, this rate is 1.2% in sporadic cases. Bilateral paragangliomas (seen in RET, VHL, NF1) are not seen with multiple paragangliomas seen in SDHC gene mutations (2).

Almost all sympathetic paragangliomas secrete norepinephrine and present themselves with hypertension, headache, sweating, and episodes of tachycardia similar to pheochromocytomas. They rarely emerge with mass effect, back/chest pain, cough, dyspnea, hoarseness, nausea after exercise, vomiting, or signs of metastatic disease. Of the parasympathetic paragangliomas, 80–90% are nonfunctional; they are localized along the glossopharyngeal and vagal nerves in the skull base and neck and emerge with mass effect (3).



Figure. Heterogeneous mass lesion containing necrotic areas in the axial CT image

CT: computed tomography

Radiological assessment is necessary for all paragangliomas, irrespective of whether they are secretory or not. Imaging is important to determine tumor localization and ensure preoperative diagnosis with a high degree of vascularity. USG, CT, MRI, and angiography may be used for diagnosis. Metaiodobenzylguanidine (MIBG) is beneficial in tumors that cannot be detected with CT and MRI or in screening tumor metastasis when malignant paragangliomas are suspected (4). Somatostatin receptor scintigraphy (SRS indium 111-pentetreotid scintigraphy, Octreoscan) can be used in diagnosis; because paragangliomas, like other neuroendocrine tumors, have high rates of somatostatin type 2 receptors on cell surfaces. PET is more sensitive than MIBG in demonstrating metastatic disease. Screening for metastatic disease should be performed in paragangliomas associated with SDHB mutation and in dopamine-secreting paragangliomas (5).

Biopsies are contraindicated because it may lead to catecholamine crisis in patients with paragangliomas. Biopsies can only be performed in patients with negative biochemical testing or in those prepared with alpha blockers. Most of paragangliomas under the neck and approximately 5% of skull base/neck paragangliomas secrete catecholamine. The definitive diagnosis of secretory paragangliomas is made with urinary and/or plasma fractionated metanephrine/catecholamine levels. For catecholamine-secreting tumors, the diagnostic values in 24-h urinary examinations are norepinephrine levels >170 mcg, epinephrine levels >35 mcg, normetanephrine levels >900 mcg, and metanephrine levels >400 mcg. Biochemical tests should be performed for all paragangliomas even though they are clinically non-functional (6).

Paragangliomas are tumors with high vascularization. They are easy to be histologically recognized; they have a thin capsule, chief cells have nuclei with central localization, and they have dense, eosinophilic, neurosecretory granules of 100–200-nm diameter in cytoplasm. Catecholamines are collected with ATP-dependent chemiosmotic process in these subcellular chromaffin granules and are stored joint to chromogranin A. In chief cells, immunohistochemical evaluations show positive staining with neuron-specific enolase, synaptophysin, and/or chromogranin; and negative staining with keratin pointing neuroendocrine nature of the tumor (7). The neuroendocrine markers of sustentacular cells are negative, but S100 or glial fibrillary acidic protein may be positive. High-grade tumors are the ones where the relationship between chief and support cells is corrupt and where support cells are lower in number. The malignancy is not easy to histologically determine (8). Nuclear polymorphism, necrosis, mitotic rate, and local invasion can also be seen in benign paragangliomas and are not diagnostic for malignancy. Although various immunohistochemical and other prognostic markers were examined, the only indicator of malignancy is metastatic spread, according to the 2004 WHO criteria (1).

The most important problems are hypertension and arrhythmia episodes that might occur during surgical excision, which is the basic treatment for these tumors. Alpha and/or beta-adrenergic blockers can be used in the preoperative preparation of patients. Excision has priority in the treatment of malignant paragangliomas; because late metastases may frequently occur. Paragangliomas most frequently metastasize to regional lymph nodes (9).

Conclusion

Pheochromocytoma/paraganglioma diagnosis should be considered in patients with complaints of palpitation, sweating, flushing, severe

headache, and/or a picture of hypertensive crisis/pulmonary edema. Abdomen USG that is a simple, easily accessible, and cheap examination should be performed firstly, catecholamine levels should be observed and surgical treatment should not be delayed to prevent a life-threatening course.

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.K., Ş.E.; Design - O.K., M.K.; Supervision - C.D., A.S.; Funding - O.K., M.Ö.G.; Materials - O.K., Ş.E.; Data Collection and/or Processing - O.K., M.K.; Analysis and/or Interpretation - Ş.E., A.S.; Literature Review - O.K., MÖG; Writer - O.K., A.S.; Critical Review - O.K., Ş.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Pathology and Genetics of Tumours of the Endocrine Organs. WHO Classification of Tumours, DeLellis RA, Lloyd RV, Heitz PU, Eng C. (Eds), IARC press, Lyon, France 2004.
2. Galan SR, Kann PH. Genetics and molecular pathogenesis of pheochromocytoma and paraganglioma. *Clin Endocrinol (Oxf)* 2013; 78: 165-75. [\[CrossRef\]](#)
3. King KS, Darmani NA, Hughes MS, Adams KT, Pacak K. Exercise-induced nausea and vomiting: another sign and symptom of pheochromocytoma and paraganglioma. *Endocrine* 2010; 37: 403-7. [\[CrossRef\]](#)
4. Baez JC, Jagannathan JP, Krajewski K, O'Regan K, Zukotynski K, Kulke M, et al. Pheochromocytoma and paraganglioma: imaging characteristics. *Cancer Imaging* 2012; 12: 153-62. [\[CrossRef\]](#)
5. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, et al. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol* 2007; 25: 2262-9. [\[CrossRef\]](#)
6. Eisenhofer G, Timmers HJ, Lenders JW, Bornstein SR, Tiebel O, Manneli M, et al. Age at diagnosis of pheochromocytoma differs according to catecholamine phenotype and tumor location. *J Clin Endocrinol Metab* 2011; 96: 375-84. [\[CrossRef\]](#)
7. Kliewer KE, Cochran AJ. A review of the histology, ultrastructure, immunohistology, and molecular biology of extra-adrenal paragangliomas. *Arch Pathol Lab Med* 1989; 113: 1209-18.
8. Eisenhofer G, Tischler AS, de Krijger RR. Diagnostic tests and biomarkers for pheochromocytoma and extra-adrenal paraganglioma: from routine laboratory methods to disease stratification. *Endocr Pathol* 2012; 23: 4-14. [\[CrossRef\]](#)
9. Moskovic DJ, Smolarz JR, Stanley D, Jimenez C, Williams MD, Hanna EY, et al. Malignant head and neck paragangliomas: is there an optimal treatment strategy? *Head Neck Oncol* 2010; 2: 23. [\[CrossRef\]](#)