Turkish Journal of Thoracic and Cardiovascular Surgery 2020;28(2):394-398
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2020.18844

*Case Report / Olgu Sunumu*

# Primary pulmonary paraganglioma: Two cases

*Primer pulmoner paraganglioma: İki olgu*

**Cabir Yüksel[1], Gökhan Kocaman[1], Bülent Mustafa Yenigün[1], Hilal Özakıncı[2], Serpil Dizbay Sak[2], Serkan Enön[1], Hakan Kutlay[1]**

[1]Department of Thoracic Surgery, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Medical Pathology, Ankara University School of Medicine, Ankara, Turkey

***ABSTRACT***

Paraganglioma is a rare tumor originating from extra-adrenal chromaffin cells. Primary pulmonary paraganglioma can also be seen in pediatric patients. Due to its endobronchial localization, morphological features, and neuroendocrine immunohistochemical profile, primary pulmonary paraganglioma can be confused with carcinoid tumor. Primary pulmonary paraganglioma should be considered in the differential diagnosis of endobronchial tumors and necessary precautions should be taken, considering that it may be functioning. In appropriate cases, bronchial sleeve resection provides curative treatment. In this article, we present two cases: First was a functioning primary pulmonary paraganglioma that underwent lobectomy and second was an entirely endobronchial tumor without any extra-bronchial spread that underwent bronchial sleeve resection.

***Keywords:*** Bronchial sleeve resection, endobronchial paraganglioma, functioning pulmonary paraganglioma, primary pulmonary paraganglioma.

***ÖZ***

Paraganglioma, ekstradrenal kromaffin hücrelerden kaynaklanan nadir bir tümördür. Primer pulmoner paraganglioma pediatrik hastalarda da izlenebilir. Endobronşial lokalizasyonu, morfolojik özellikleri ve nöroendokrin immünhistokimyasal profili nedeniyle primer pulmoner paraganglioma karsinoid tümör ile karıştırılabilir. Endobronşiyal tümörlerin ayırıcı tanısında primer pulmoner paraganglioma düşünülmeli ve fonksiyonel olabileceği göz önünde bulundurularak gerekli önlemler alınmalıdır. Uygun olgularda, bronşiyal sleeve rezeksiyon küratif tedavi sağlar. Bu yazıda, iki olgu sunuldu: İlki lobektomi uygulanan fonksiyonel bir primer pulmoner paraganglioma, ikincisi bronşiyal sleeve rezeksiyon uygulanan, ekstrabronşiyal yayılımı olmayan, tamamen endobronşiyal bir tümör idi.

***Anahtar sözcükler:*** Bronşiyal sleeve rezeksiyon, endobronşiyal paraganglioma, fonksiyonel pulmoner paraganglioma, primer pulmoner paraganglioma.

Paraganglioma is a rare tumor originating from extra-adrenal chromaffin cells. Its incidence is around two-eight cases per million population. Primary pulmonary paragangliomas (PPPs) are even rarer. Paragangliomas in the head, neck, and anterior mediastinum are usually non-secreting and do not produce catecholamines that cause symptoms such as hypertension.[1] In this article, we present two cases of PPP. First was a functioning PPP that underwent lobectomy and second was totally endobronchial, so we performed bronchial sleeve resection.

## CASE REPORT

***Case 1-*** A 15-year-old male patient with cough, weakness, and hemoptysis had a thorax computed tomography (CT) and a 3-cm lesion in the lower lobe of the left lung was detected (Figure 1a). Bronchoscopy revealed a hyper-vascularized lesion in the apical segment bronchus of the left lower lobe. Hypertension (200/100 mmHg) and tachycardia (170 beats/min) were observed during the biopsy and the procedure was cancelled. Urine and blood noradrenaline levels were found to be high (3,100 µg/day and

*Received:* October 03, 2019 *Accepted:* November 23, 2019 *Published online:* April 22, 2020

**Correspondence:** Gökhan Kocaman, MD. Ankara Üniversitesi Tıp Fakültesi Göğüs Cerrahisi Anabilim Dalı, 06590 Çankaya, Ankara, Türkiye.
Tel: +90 312 - 508 29 17 e-mail: gkhnkcmn@hotmail.com

***Cite this article as:***
Yüksel C, Kocaman G, Yenigün BM, Özakıncı H, Dizbay Sak S, Enön S, et al. Primary pulmonary paraganglioma: Two cases. Turk Gogus Kalp Dama 2020;28(2):394-398

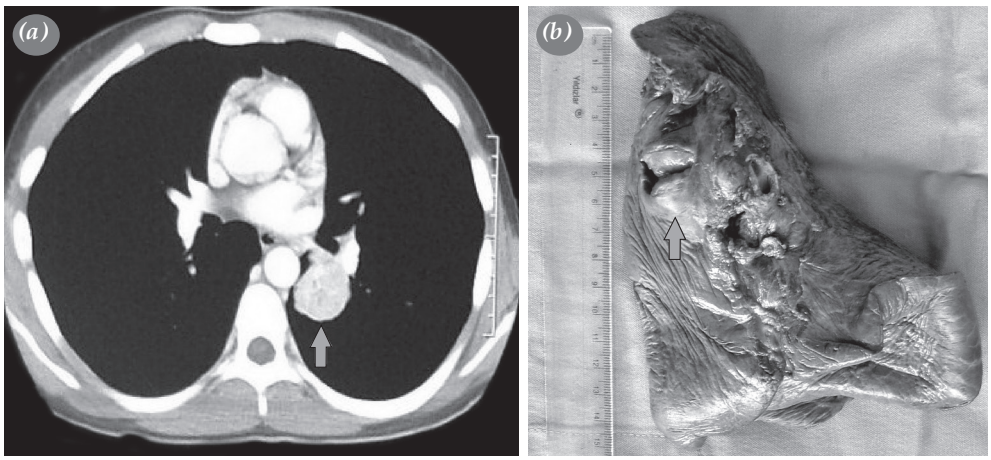


**Figure 1. (a)** Axial computed tomography image of mass and **(b)** resection specimen (gray arrows show mass).

503 ng/L, respectively), while adrenaline levels were normal. Urinary vanillylmandelic acid (VMA) (26.6 mg/day), homovanillic acid (HVA) (7.5 mg/day), and normetanephrine levels (11,039 µg/day) were also found to be high. Abdominal CT, adrenal CT, technetium-99m bone scintigraphy, scrotal ultrasonography, and 131I metaiodobenzylguanidine scintigraphy results were normal. Indium-111 octreotide scan showed focal increased activity in the medial aspect of the left lung, more prominent in the posterior position. Symptoms and findings were consistent with PPP. In the preoperative period, hypertension was controlled with propranolol and doxazosin mesylate. The patient underwent left thoracotomy with lower lobectomy and mediastinal lymph node sampling. In order to avoid intraoperative catecholamine release, parenchymal manipulation was minimized during exploration. Lower lobe vein was found and clamped first, and then lobectomy was completed in usual manner. After resection,

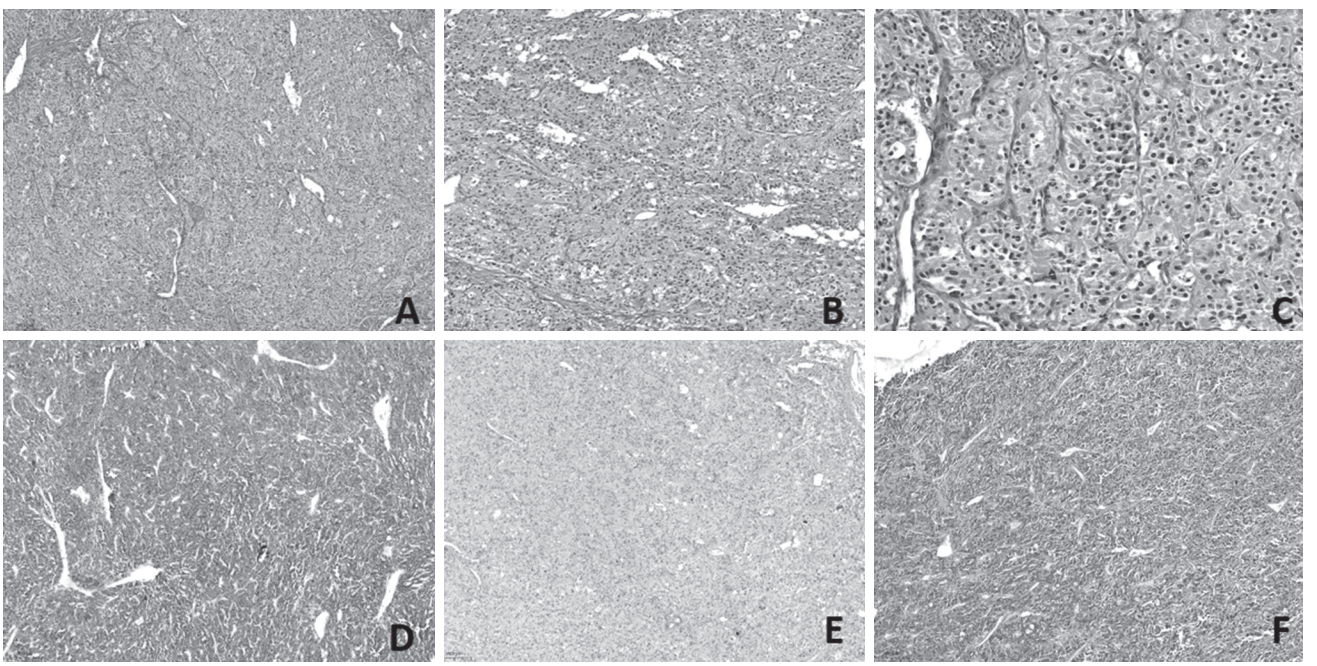


**Figure 2.** Case 1. Tumor cells with amphophilic cytoplasm showing nested pattern within vascular network on hematoxylin and eosin stain [**(a)** ×50, **(b)** ×100, **(c)** ×200]. Tumor cells were positive for synaptophysin [**(d)** ×50], GATA3 [**(e)** ×50], and tyrosine hydroxylase [**(f)** ×50].

0.1 mg/kg sodium nitroprusside was started for blood pressure control.

On macroscopic examination, an endobronchial well-demarcated tumor with yellow-brown cut surface was seen (Figure 1b). In microscopic examination, tumor cells were distributed in nested pattern, with round/oval nucleus and abundant granular amphophilic cytoplasm, within vascular networks. Scattered pleomorphic cells with atypical nuclei were observed, but there was no necrosis or mitosis. Tumor cells were positive for chromogranin A, synaptophysin, GATA3, and tyrosine hydroxylase and negative for cytokeratin (CK) (AE1+AE3) and thyroid transcription factor-1 (TTF-1) (Figure 2). Morphological and immunohistochemical features were supporting the diagnosis of paraganglioma. Tumor was moderately differentiated (score 5) when evaluated for the grading system for adrenal pheochromocytoma and paraganglioma (GAPP) retrospectively. No metastasis was detected in lymph nodes. In the first month control, blood noradrenaline levels (222 ng/L), urine VMA and HVA levels (2.7 mg/day and 3.3 mg/day, respectively), and blood pressure were within normal limits. The patient has been followed-up for 10 years without recurrence. A written informed consent was obtained from the legal guardian of the patient.

***Case 2-*** A 32-year-old male patient with a history of 12 pack/year smoking had dyspnea for one year. Thorax CT revealed a 13-mm lesion within the left main bronchus (Figure 3a) and bronchoscopy revealed a bright red colored lesion with a smooth surface that completely occluded the left main bronchus (Figure 3b). The positron emission tomography/CT scan showed maximum standardized uptake value of 8.2 involvement only in the lesion and resection was planned with the preliminary diagnosis of carcinoid tumor. The patient underwent left thoracotomy with bronchial sleeve resection and mediastinal lymph node dissection. Intraoperative frozen-section was interpreted as "neuroendocrine tumor with marked pleomorphism without mitosis". Tumor had a graytan cut surface; on histological examination, round/oval or elongated tumor cells with abundant granular amphophilic/basophilic cytoplasm, arranged in nests and trabeculae were noted. Tumor cell nests were surrounded by a capillary network. Marked nuclear pleomorphism was seen while there was no mitotic activity or necrosis. Tumor cells were positive for chromogranin A, synaptophysin, CD56, GATA3, and tyrosine hydroxylase and negative for CK and TTF-1. Sustentacular cells surrounding the nests were S100 positive (Figure 4). Succinate dehydrogenase complex flavoprotein subunit A (SDHA) and succinate dehydrogenase complex iron sulfur subunit B (SDHB) were positive in the tumor, immunohistochemically. Tumor was diagnosed as PPP with morphological, immunohistochemical, and clinical findings. Tumor was moderately differentiated with a GAPP score of 3. Next generation sequencing (NGS) was performed on formalin-fixed paraffin-embedded tumor tissue and a missense mutation (c.889C>T, p.P297S) in SDHA gene with 56% allelic fraction (AF) and two missense mutations (c.2071G>A, p.G691S, AF: 49% and c.972G>C, p.W324C, AF: 53%) in RET (rearranged during transfection) gene were detected. There were no mutations in SDHB and SDHD genes. As the significance of these mutations was uncertain and AFs were suspected to be of germline origin, genetic counseling was suggested. No tumor was observed in bronchial surgical margins and lymph nodes. The patient was discharged on the fifth postoperative day without any problem. Follow-up has been continuing in

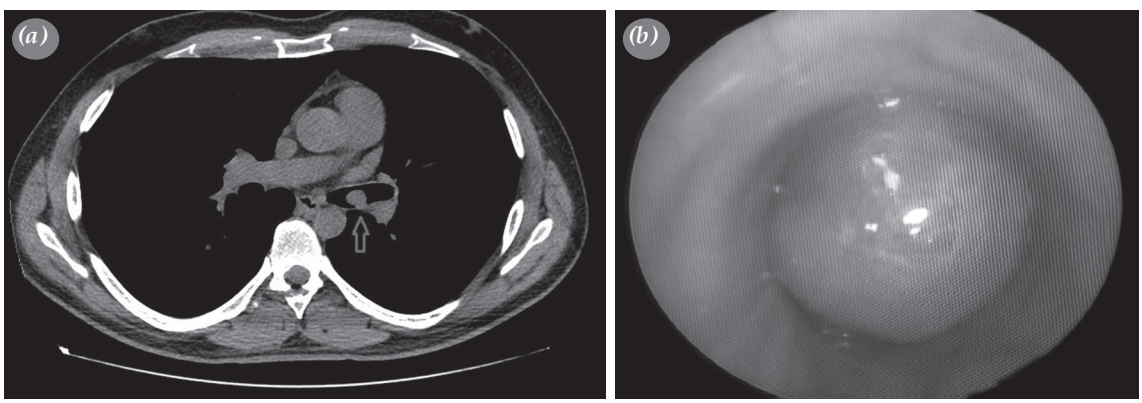


**Figure 3. (a)** Axial computed tomography image of endobronchial mass (gray arrow shows mass) and **(b)** bronchoscopic view of mass.

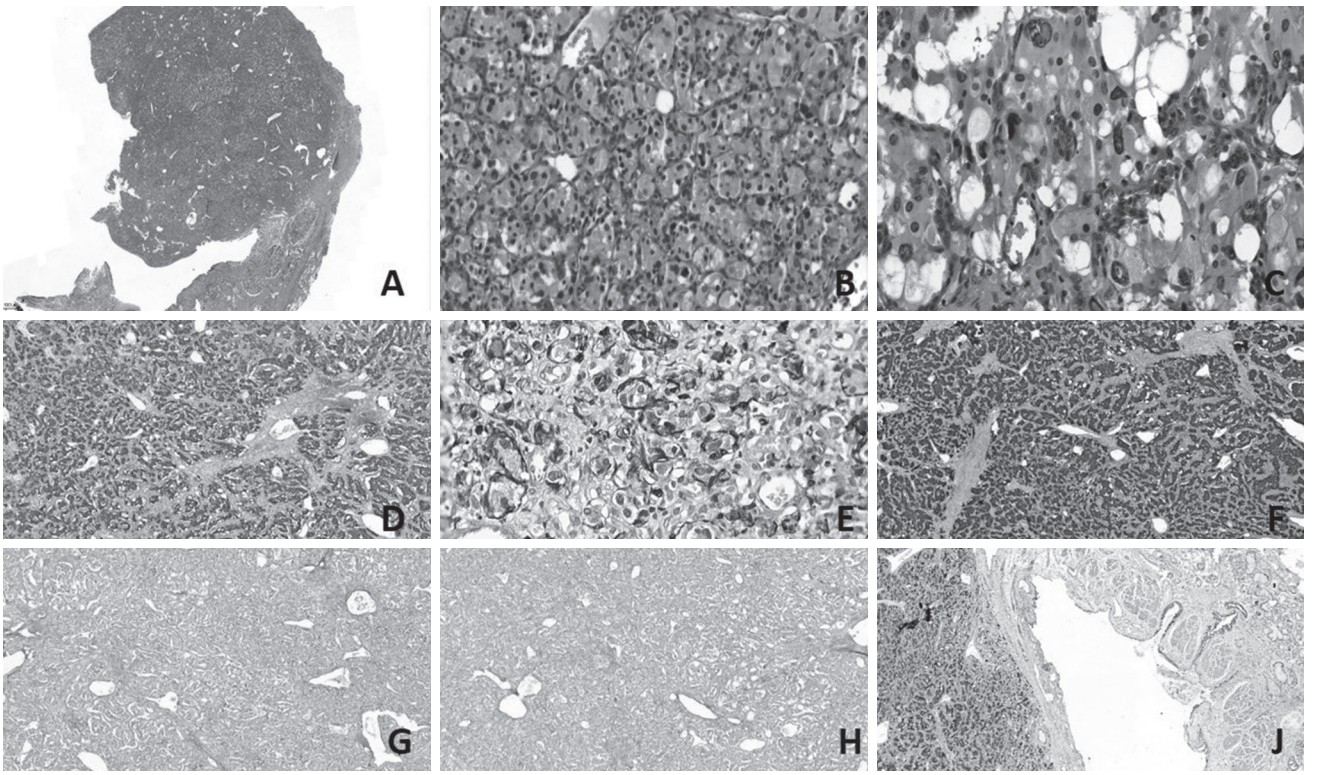


**Figure 4.** Case 2. Endobronchial tumor showed nested pattern with marked pleomorphism on hematoxylin and eosin stain [**(a)** ×40, **(b)** ×100, **(c)** ×200]. Tumor cells were positive for synaptophysin [**(d)** ×100] and sustentacular cells showed S100 positivity [**(e)** ×200]. Tumor cells were also positive for tyrosine hydroxylase [**(f)** ×100] Pan-cytokeratin [**(g)** ×100] and thyroid transcription factor-1 [**(h)** ×100] were negative in tumor cells. Succinate dehydrogenase complex flavoprotein subunit A expression was preserved [**(j)** ×50).

the ninth month without any recurrence or additional therapy. A written informed consent was obtained from the patient.

## DISCUSSION

The first PPP case was published by Heppleston[2] in 1958 and the total number of cases published to date is less than 50. Pulmonary paragangliomas usually do not cause systemic symptoms and the majority are detected incidentally.[3] There is only one case in the literature that describes functioning PPP with high catecholamine levels.[4] In this case, hypertension was observed in the preoperative period while in our case, hypertension in the form of an attack triggered by manipulation was observed. In this respect, our first case constitutes the second functioning PPP and also the second pediatric case in the literature, as only one other case has been described in this age group before.[5]

Endobronchial PPPs can be diagnosed at an earlier stage as in our cases with complaints such as cough, hemoptysis, and shortness of breath. Bronchial sleeve resection can be performed in endobronchial PPPs. There are only two cases in the literature that underwent bronchial sleeve resection for endobronchial PPP.[5,6] Both of them were in the left main bronchus and tumors were resected with negative surgical margins as in our second case. No recurrence was observed in these two cases described in the literature and our patient also has had an uneventful follow-up so far.

Primary pulmonary paragangliomas are extremely rare and their distinction from epithelial neuroendocrine tumors is important because clinical and biochemical features and genetic implications are different. The rate of germline susceptibility of paraganglioma is almost 40%. Risk of multifocal and metastatic disease and possibility of synchronous tumors other than paraganglioma (e.g., renal cell carcinoma, thyroid carcinoma) increase in SDH related disease. To determine the SDH related tumors, immunohistochemical evaluation of SDHA and SDHB protein expressions are recommended.[7] In our second case, both SDHA and SDHB expressions were preserved suggesting unaltered SDH function, although a missense mutation of uncertain significance

was detected in SDHA gene by NGS. Similar to our case, there are some paraganglioma cases in the literature that show no loss of expression in SDHA protein despite some mutations in SDHA gene.[8] Unfortunately, we could not analyze our first case with regard to SDH genes.

Distinction from a carcinoid tumor, which is a PPP's major clinical/histological mimicker, can be impossible without the use of CKs and tyrosine hydroxylase, unless it is morphologically suspected. In neuroendocrine tumor diagnosis, the importance of keratins, which are available in almost every pathology laboratory, should be emphasized. However, pulmonary gangliocytic paragangliomas that can show CK positivity should also be kept in mind.[6] Tyrosine hydroxylase and GATA3 are new markers that are helpful in the differential diagnosis.

In conclusion, primary pulmonary paraganglioma is a rare lung tumor that can be seen in pediatric patients. Due to its localization, morphological features, and neuroendocrine immunohistochemical profile, it can mimic carcinoid tumor. Primary pulmonary paragangliomas should be considered in the differential diagnosis of endobronchial tumors and necessary precautions should be taken considering that it may be functioning. In appropriate cases, bronchial sleeve resections provide curative treatment.

**Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding**

The authors received no financial support for the research and/or authorship of this article.

## REFERENCES

1. Erickson D, Kudva YC, Ebersold MJ, Thompson GB, Grant CS, van Heerden JA, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. J Clin Endocrinol Metab 2001;86:5210-6.
2. Heppleston AG. A carotid-body-like tumour in the lung. J Pathol Bacteriol 1958;75:461-4.
3. Kavakli K, Ozturk M, Ongoru O, Gürkök S, Genc O. Primary pulmonary paraganglioma with Hodgkin's lymphoma. Thorac Cardiovasc Surg 2009;57:375-7.
4. Shibahara J, Goto A, Niki T, Tanaka M, Nakajima J, Fukayama M. Primary pulmonary paraganglioma: report of a functioning case with immunohistochemical and ultrastructural study. Am J Surg Pathol 2004;28:825-9.
5. Geoffrion TR, DeKeyzer L, Shah G, Nair SJ, Pirolli TJ, Kernstine K. Pulmonary paraganglioma in a 10-year-old: a case report and review of the literature. J Surg Case Rep 2018;2018:rjy047.
6. Aubertine CL, Flieder DB. Primary paraganglioma of the lung. Ann Diagn Pathol 2004;8:237-41.
7. Asa SL, Ezzat S, Mete O. The Diagnosis and Clinical Significance of Paragangliomas in Unusual Locations. J Clin Med 2018;7. pii: E280.
8. van der Tuin K, Mensenkamp AR, Tops CMJ, Corssmit EPM, Dinjens WN, van de Horst-Schrivers ANA, et al. Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study. J Clin Endocrinol Metab 2018;103:438-45.