Case Report

Pheochromocytoma of the organ of Zuckerkandl

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A B S T R A C T

Paragangliomas are uncommon neuroendocrine neoplasms that occur in characteristic locations associated with the paraganglionic system [1]. While parasympathetic paragangliomas are mainly located at the head and neck, sympathetic paragangliomas are mostly located below the neck [2]. Among parasympathetic paragangliomas, pheochromocytomas are the most common. Ninety percent of cases of pheochromocytomas arise within the adrenal gland. We report a case of a 63-year-old woman with an extra-adrenal pheochromocytoma of the organ of Zuckerkandl detected by CT and MRI and subsequently confirmed by postoperative histology and immunohistochemistry.

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Introduction

Paragangliomas are uncommon neuroendocrine neoplasms that occur in characteristic locations associated with the paraganglionic system [1]. While parasympathetic paragangliomas are mainly located at the head and neck, sympathetic paragangliomas are mostly located below the neck [2]. Among parasympathetic paragangliomas, pheochromocytomas are the most common. Pheochromocytomas and other sympathetic paragangliomas are catecholamine secreting neuroendocrine tumors (NET) [3]. Classic clinical presentations of these tumors include headache, palpitation, and diaphoresis [4]. Approximately 85% of these masses occur within the adrenal glands, whereas 15% are located extra-adrenally along the sympathetic chain [5]. Up to 98% of extra-adrenal diseases is intra-abdominal, most frequently arise from the organ of Zuckerkandl [6]. Since the imaging features, clinical manifestations, histologic appearances of this entity are variable, making diagnosis a challenge. We report a rare case of extra-adrenal pheochromocytoma of the organ of Zuckerkandl, which is confirmed by postoperative histopathology immunohistochemistry.

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Case report

A 63-year-old female patient presented with complaint of epigastric pain for approximately 1 month. In the past 4 years, she was diagnosed with pancreatic carcinoma and had undergone a distal pancreatectomy and splenectomy. The patient also had a history of hypertension and gastroesophageal reflux disease. On physical exam, she appeared in no distress and was mildly hypertensive with otherwise normal vital signs. Abdominal exam revealed no abdominal mass or organomegaly. Laboratory investigations showed normal findings (complete blood count, serum electrolytes, urinalysis, thyroid, liver and renal functions). Imaging was obtained to further evaluate the abdominal pain. Contrast-enhanced abdominal CT scan revealed a 52 × 29 × 27mm well-defined, vividly enhancing soft tissue mass on the right side of aorta, closing to the bifurcation. MRI was then performed, showing a T1W-hypointense, T2W-hyperintense heterogeneous mass within the retroperitoneum, on the right side of aorta. Vivid enhancement after intravenous gadolinium administration was noted (Figs. 1 and 2). The mass showed increased intensity on diffusion-weighted imaging and reduced apparent diffusion coefficient values, which is consistent with restricted diffusion (Fig. 3). The lesion maintained its signal intensity on out-of-phase images (Fig. 4). Also, multiple punctate flow voids were noted on T1- and T2-weighted images. The patient underwent a complete en bloc removal of the mass. Microscopically, hematoxylin–eosin staining of the tumor tissue showed that the mass includes chief cells with basophilic cells and sustentacular cells. Cytoplasmic hyaline globules were also present. Immunohistochemical staining showed the tumor tissue was positive for chromogranin A, synaptophysin, S100, CD34, and vimentin. Meanwhile, the tumor tissue was negative for calretinin, HMB45, CK7, CK20, and desmin (Figs. 5–7). Collectively, these results indicated that the diagnosis of the tumor was extra-adrenal pheochromocytoma. Informed consent was given by the patient.

Discussion

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare catecholamine-secreting tumors originating from
Fig. 3 – This mass has high-signal intensity on DWI (A) and low ADC values (B), consistent with diffusion restriction.

Fig. 4 – Axial T1-weighted in-phase (A) and out-of-phase (B) MR images show lesion with no signal intensity drop on out-of-phase image.

cromaffin cells of the adrenal medulla or extra-adrenal paraganglia [7]. These tumors arise within the adrenal glands in approximately 85% of cases. In the remaining 15% of cases, tumors originate from extra-adrenal paraganglionic chromaffin tissues and are referred to as extra-adrenal PCCs or PGLs [8,9]. Depending on the anatomic site and secretory products, PGLs are categorized into parasympathetic and sympathetic subtypes. According to the World Health Organization Classification of Tumors, updated in 2017, “A pheochromocytoma is an intra-adrenal sympathetic paraganglioma” [10,11]. Approximately 98% of sympathetic PGLs are found below the diaphragm, in association with the celiac, superior mesenteric, inferior mesenteric ganglia, and organ of Zuckerkandl. The organ of Zuckerkandl, which is a group of paraganglia located in the interaortocaval region from the superior mesenteric artery or renal arteries to aortic bifurcation, is the most frequent location [12]. Clinically, diverse presentations of FCC and PGL are related to the hypersecretion of catecholamines, typically producing paroxysmal symptoms, hypertension, and suprarenal or midline abdominal masses. The classic triad of extra-adrenal pheochromocytoma includes paroxysmal attacks of headache, palpitations, and diaphoresis [9,10,13]. Differential diagnosis includes other abdominal masses, especially malignant tumors. Pheochromocytoma has been called the “ten percent” tumors based on the fact that 10% of the cases are bilateral, 10% are extra-adrenal, 10% are clinically silent, and 10% of intra adrenal PCCs are malignant [14].

The imaging findings of FCCs are variable due to the presence of internal necrosis, cystic degeneration, and hem-
orrhage [15]. Unenhanced CT may show well-defined mass with attenuation usually higher than 10HU, differentiating it from an adrenal adenoma. Contrast-enhanced CT may demonstrate vivid enhancement with variable washout patterns due to rich capillary network. Although MRI features of PCC are also variable because of the previously mentioned factors, the most common appearance is a mass with "light bulb" hyperintensity on T2W imaging and hypointensity on T1W imaging. Lesion typically show strong enhancement after gadolinium administration [16,17]. However, it is noted that a very high lesion signal intensity on T2W sequences is not pathognomonic for PCCs. Additionally, only approximately 65% of cases are correctly diagnosed as PCCs, whereas 35% are misclassified as malignant lesions or benign adenomas due to the lack of high signal intensity at T2W imaging. Punctate flow-voids representing tumor vessels are referred to as “salt-and-pepper” pattern characteristically seen on T1- and T2-weighted images. The tumors commonly do not

Fig. 5 – Hematoxylin – eosin staining x100 (A) and x400 (B) of the tumor tissue demonstrates that the mass includes chief cells with basophilic cells and sustentacular cells, creating “Zellballen” pattern.

Fig. 6 – Immunohistochemical result show positive for chromogranin A (A), synaptophysin (B), S100 (C), IHC x100.

Fig. 7 – Calretinin (A), HMB45 (B) and desmin (C) negative, IHCx40.
contain a large amount of intracellular lipid so they will not
demonstrate signal loss on out-of-phase sequences [16–18].

In histological studies, PCCs and PGLs are made up of chief
cells or pheochromocytes and “supporting” cells or sustentac-ular cells. These cells may present several different patterns,
“Zellballen” or cell-nesting and trabecular patterns are seen
most [9,13,19]. Immunohistochemically, the chief cells of
the tumor are positive for chromogranin A and synaptophysin,
which are the most common generic neuroendocrine markers,
meanwhile, the sustentacular cells express S100 protein [4,20].
The most mentioned pathological differential diagnosis of
PGLs presenting in the abdominal cavity are other NET, espe-
cially in the setting of concurrent pancreatic carcinoma, such
as this case. Both PCCs/PGLs and NET show positive staining
for chromogranin A and synaptophysin. However, the absence
of positivity for cytokeratins such as CK7, CK20, CAM5.2,…help
to distinguish them from NET [4].

The term “malignant pheochromocytoma” and “benign
pheochromocytoma” from the 2004 WHO classification of
endocrine tumors are no longer used. According to the
2017 WHO classification of endocrine tumors, all PCCs/PGLs
could have metastatic potential and several factors may be
used to stratify the risk. Currently, no individual scheme
stratifying metastatic risk has been officially recommended.
However, some immunohistochemical markers, such as Ki-67
proliferative index and SDHB, may be used to identify risk
stratification [4,20,21]. A seminal study of PCCs and sympa-
thetic PGLs by Linnoila et al. in 1990 demonstrated 4 adverse
factors: extra-adrenal location, confluent necrosis, coarse
nodularity, and absence of hyaline globules. The most power-
ful predictor among these factors is extra-adrenal location,
which is known to correlate with SDHB [19,20]. In 2005, a
scoring system called GAPP was developed by Kimura et al.
GAPP scores based on histological, immunohistochemical,
and biochemical characteristics to predict the metastatic
potential of tumors and the patients’ prognosis with tumors
that metastasize [19].

The optimal treatment of pheochromocytoma is surgical
resection. Before the operation, antihypertensive medications
are often given to lower blood pressure and prevent
hypertensive crisis during operation. In patient with malignant
disease, palliative chemotherapy, and radiation therapy is indi-
cated [8,22].

Conclusion

PCCs and PGLs are unusual tumors that occur in charac-
teristic anatomic sites and are often detected by imaging exami-
nation. The disease presenting with a variability of clinical man-
ifestations and imaging findings makes it challenging to di-
agnose correctly. Immunohistochemical studies have impor-
tant roles in both the pathologic diagnosis and prognosis of
PCC/PGL.

REFERENCES

[1] Asa SL, Ezzat S, Mete O. The diagnosis and clinical
significance of paragangliomas in unusual locations. J Clin
Med 2018;7(9).
[2] Lee KY, Oh Y-W, Noh HJ, et al. Extra-adrenal paragangliomas
of the body: imaging features. Am. J. Roentgenol. 2006;187(2):492–504.
[3] Manger WM, Gifford RW. Pheochromocytoma. J Clin
Hypertens (Greenwich) 2002;4(1):62–72.
[4] Cheung VKY, Gill AJ, Chau A. Old, new, and emerging
immunohistochemical markers in pheochromocytoma and
paraganglioma. Endocr Pathol 2018;29(2):169–75.
[5] Das CJ, Baruah MP, Baruah UM. Radiological imaging in
diagnostic endocrine hypertension. Indian J EndocrinoMetab
2011;15(Suppl4):S383–8.
[6] Whalen RK, Althausen AF, Daniels GH. Extra-adrenal
pheochromocytoma. J. Urol. 1992;147(1):1–10.
[7] Aygun N, Uludag M. Pheochromocytoma and paraganglioma:
from epidemiology to clinical findings. Sisli Etfal Hastan Tip
Bul 2020;54(2):159–68.
[8] Chen H, Sippel RS, O’Dorisio MS, et al. The North American
Neuroendocrine Tumor Society consensus guideline for the
diagnosis and management of neuroendocrine tumors:
pheochromocytoma, paraganglioma, and medullary thyroid
cancer. Pancreas 2010;39(6):775–83.
[9] Whalen RK, Althausen AF, Daniels GH. Extra-adrenal
pheochromocytoma. J. Urol. 1992;147(1):1–10.
[10] Barnes L, Eveson JW, Reichart P, et al. World Health
Organization Classification of Tumours. Pathology and
Genetics of Head and Neck Tumours. IARC Press Lyon; 2005.
[11] Lam AK. Update on Adrenal Tumours in 2017 World Health
Organization (WHO) of Endocrine Tumours. Endocr Pathol
2017;28(3):213–27.
[12] Cancer TIAfor R. on. Pathology and Genetics of Head and
Neck Tumours. Lyon: World Health Organization; 2005.
[13] Thompson LDR. Pheochromocytoma:. Pathology Case
Reviews 2005;10(5):243–51.
[14] Rha SE, Byun JY, Jung SE, et al. Neurogenic tumors in the
abdomen: tumor types and imaging characteristics.
Radiographics 2003;23(1):29–43.
[15] Katabathina VS, Rajebi H, Chen M, et al. Genetics and imaging
of pheochromocytomas and paragangliomas: current update.
Abdom Radiol 2020;45(4):928–44.
[16] Blake MA, Kalra MK, Maher MM, et al. Pheochromocytoma:
an imaging chameleon. Radiographics 2004;24(suppl. 1):S87–99.
[17] Shankar P, Heller MT. Multi-modality imaging
of pheochromocytoma. Radiology Case Reports 2012;7(4):770.
[18] Leung K, Stamm M, Raja A, et al. Pheochromocytoma: the
range of appearances on ultrasound, CT, MRI, and functional
imaging. Am. J. Roentgenol. 2013;200(2):370–8.
[19] Tischler AS. Pheochromocytoma and extra-adrenal
paraganglioma: updates. Arch Pathol Lab Med 2008;132:13.
[20] Tischler AS, deKrijger RR. 15 YEARS OF PARAGANGLIOMA:
Pathology of pheochromocytoma and paraganglioma.
Endocr. Relat. Cancer 2015;22(4):T123–33.
[21] Clarke MR, Weyant RJ, Watson CG, et al. Prognostic markers
in pheochromocytoma. Hum. Pathol. 1998;29(5):522–6.
[22] Chrisoulidou A, Kaltzas G, Ilias I, et al. The diagnosis and
management of malignant pheochromocytoma and
paraganglioma. Endocr Relat Cancer 2007;14(3):569–85.