

Adrenal hemangioblastoma

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Hemangioblastoma (HB) is a rare benign tumor that most commonly occurs in the cerebellum. HB is composed of neoplastic stromal cells and abundant small vessels. However, the exact origin of stromal cells is controversial. Extranural HBs have been reported in a small series, and peripheral HBs arising in the adrenal gland are extremely rare. Herein, we report a case of sporadic adrenal HB in a 54-year-old woman. The tumor was a well-circumscribed, yellow mass measuring 4.2 cm in diameter. Histologically, the tumor was composed of small blood vessels and vacuolated stromal cells with clear cytoplasm. On immunohistochemical stain, the stromal cells were positive for S-100 protein, neuron-specific enolase, and synaptophysin. The tumor did not reveal mutation of VHL alleles. We herein present a case of HB of the adrenal gland and review of the literature.

Key Words: Hemangioblastoma; Adrenal glands; von Hippel-Lindau disease; Immunohistochemistry; Sequencing

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Hemangioblastoma (HB) is a rare benign tumor of the central nervous system that commonly occurs in the cerebellum. While these tumors occur sporadically in most cases, 25% of the patients with HBs are associated with von Hippel-Lindau (VHL) syndrome. Sporadic HBs generally occur in adults between 30 and 65 years of age, whereas VHL-associated tumors present in younger patients, at age 20–30 years [1]. In rare cases, HBs have been reported to occur in extraneural tissue such as the liver, lungs, pancreas, retroperitoneum, soft tissues, and kidney [2-5]. To the best of our knowledge, only five such cases have yet been reported in the literature (Table 1) [3,6-8]. Herein, we present a case of sporadic adrenal HB in a 54-year-old female patient.

CASE REPORT

An adrenal mass was incidentally detected in a 54-year-old woman during a regular medical check-up. She did not have a history of pancreatic tumor, renal tumor, or adrenal tumor. Her family members had no history of such diseases. Laboratory investigations were performed, and 24-hour urinary metanephrine

(0.4 mg/day), vanillylmandelic acid (3.3 mg/day), homovanillic acid (4.1 mg/day), and 17-ketosteroid level (16.8 mg/day) were within normal limits. Plasma aldosterone concentration (PAC) was 10.5 ng/dL, plasma renin activity (PRA) was 0.42 ng/mL per hour, and PAC/PRA ratio was 25 ng/dL per ng/mL/hr. Magnetic resonance imaging revealed a 4.2 × 4.2 × 3.6 cm well-defined mass in the left adrenal gland, which was suspected to be a hemangioma (Fig. 1A). The patient underwent partial adrenalectomy. Macroscopic examination revealed that the nodular mass weighed 21 g and displayed a brown-colored cut surface with hemorrhage (Fig. 1B).

On histological examination, the tumor was well encapsulated by a fibrous wall. At low magnification, hypocellular and hypercellular area were present. The tumor was composed of abundant small blood vessels admixed with stromal cells. The blood vessels were lined by thin endothelial cells. The stromal cells had clear and vacuolated or pale eosinophilic cytoplasm (Fig. 2). Their nuclei were round to ovoid, with occasional nuclear atypia. There was no evidence of necrosis. On immunohistochemical stain, the stromal cells were positive for S-100 protein, synaptophysin, and neu-

Table 1. Reported cases of hemangioblastoma of the adrenal gland in the literature

Case	Age (yr)/ Sex	Clinical feature	Size/Weight	Microscopic findings	Immunohistochemical or special stain/EM	Association with VHL syndrome	Follow-up
Burns et al. (1987) [6]	23/F	Erythrocytosis (hematocrit, 58%)	5.0 cm	Abundant thin-walled blood vessels; stromal cells, large cells with vacuolated clear cytoplasm	Stromal cell with fat vacuole	Yes	NA
Itoh et al. (1988) [7]	49/M	Incidentally found; elevated noradrenalin (187.4 µg/day) and dopamine (2,308 µg/day) in urine	2.7 cm	Abundant capillary structures; stromal cells, large ovoid	NSE (+), fat stain (+)	No	NA
Nonaka et al. (2007) [3]	30/F	Cerebellar and spinal HB, bilateral adrenal HB	0.9 cm; 0.5 cm	Focal cavernous vascular spaces; stromal cells, vacuolated large with amphophilic cytoplasm, round to oval nuclei	S-100 protein (+, focal), chromogranin (+), CD31 (-), CD34 (-)	Yes	NA
Browning and Parker (2008) [8]	30/M	Bilateral adrenal HB, spinal and cerebellar HB, pancreatic and renal cysts, cystic renal cell carcinoma (suspicious)	Not identified (12.5 g; 8.3 g)	Abundant capillaries; stromal spindle cells. Stromal cells; large, intimately connected with vascular walls	Chromogranin (+), vimentin (+), S-100 protein (-)	Yes	NA
Current case	54/F	Incidentally found	4.2 cm	Abundant capillaries; stromal cells, vacuolated or amphophilic cytoplasm	CD34 (-), CD31 (-), inhibin-alpha (-), EMA (-), CK (-), CA-9 (-), CD10 (-), S-100 protein (+), synaptophysin (+), NSE (+)	No	Alive (1 yr)

EM, electron microscopy; VHL, von Hippel-Lindau; F, female; NA, not available; M, male; NSE, neuron-specific enolase; HB, hemangioblastoma; EMA, epithelial membrane antigen; CK, cytokeratin; CA-9, carbonic anhydrase 9.

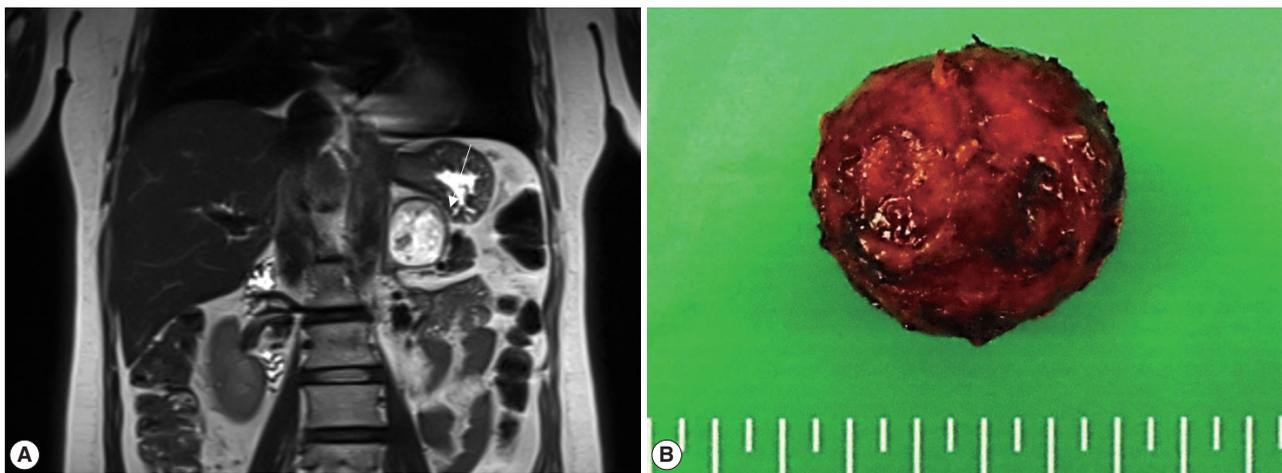


Fig. 1. (A) Magnetic resonance imaging reveals a 4.2 × 3.6 × 4.2 cm mass in the left adrenal gland. (B) Gross examination shows an encapsulated nodular mass.

ron-specific enolase (NSE). The endothelial markers, CD34 and CD31, highlighted blood vessels (Fig. 3). The stromal cells were negative for inhibin- α , epithelial membrane antigen (EMA), carbonic anhydrase 9 (CA-9), CD10, glial fibrillary acidic protein (GFAP), GATA3, and chromogranin A. The tumor was diagnosed as HB based on the histological and immunohistochemical findings. The adrenal tissue surrounding the tumor was not submitted.

Targeted sequencing was performed using the ONCOaccu-Panel (NGeneBio, Seoul, Korea) which covers 323 genes. Capicua

transcriptional repressor (*CIC*), folliculin (*FLCN*), fms related receptor tyrosine kinase 1 (*FLT1*), poly (ADP-ribose) polymerase 1 (*PARP1*), and polybromo 1 (*PBRM1*) were mutated. However, *VHL* was not mutated (Table 2). The patient survived with no evidence of tumor recurrence at 1-year follow-up.

DISCUSSION

HB is a rare benign tumor that generally occurs in the cere-

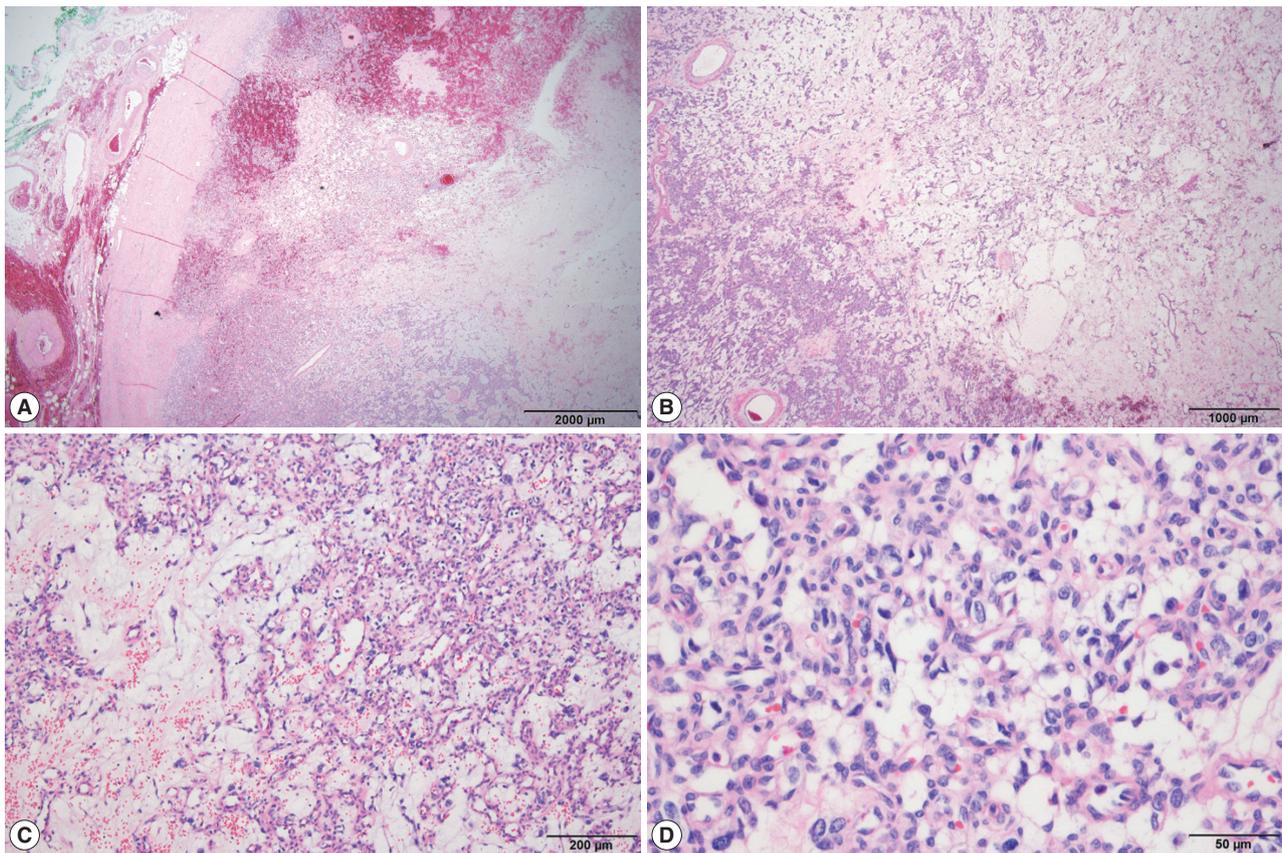


Fig. 2. The tumor is encapsulated by a fibrous wall (A) and is composed of alternating hypercellular and hypocellular areas (B). Vascular structures with vacuolated stromal cells (C, D) are observed.

bellum in adults. In rare cases, HB has been reported to occur at extracerebellar sites. The unusual anatomical locations and histopathological features of HB may pose a diagnostic challenge. HB has been considered as a vascular neoplasm because of the histological findings of its vascular structure. However, various cell lineages such as glial (GFAP), neural (S-100 protein and NSE), vascular, endothelial (factor XIIIa), mesenchymal (vimentin), epithelial (cytokeratin), and smooth muscle/myofibroblastic (desmin and calponin) have been proposed on the bases of immunohistochemical findings [9-12]. Until now, their cell lineage remains unknown.

Somatic inactivation of both *VHL* alleles and the subsequent loss of VHL protein are found in patients with HBs and nonhereditary clear cell renal cell carcinomas (RCCs) [13]. The present case revealed wild-type *VHL* alleles in targeted sequencing. However, mutations of *CIC*, *FLCN*, *FLT1*, *PARP1*, and *PBRM1* were found (Table 2). *CIC* is a member of the high-mobility-group-box superfamily of transcriptional repressors. Mutation of *CIC* is associated with oligodendrogliomas [14], and fusions of *CIC* with *DUX4* (double homeobox 4) and *FOXO4* (forkhead

box O) genes have been reported in patients with round cell sarcomas [15]. *FLCN* mutation is associated with Birt-Hogg-Dubé syndrome, which is characterized by benign skin tumors, lung cysts, and kidney lesions [16]. *FLT1* encodes a member of the vascular endothelial growth factor receptor family, which plays an important role in angiogenesis and vasculogenesis. *PARP1* encodes poly(ADP-ribose)transferase, which is involved in cell differentiation, proliferation, recovery from DNA damage, and tumor transformation. *PARP1* mutation is associated with Fanconi anemia [17]. *PBRM1* encodes a subunit of ATP-dependent chromatin-remodeling complexes, and *PBRM1* mutation is associated with clear cell RCC [18] and epithelioid sarcoma [19]. It is unclear whether these mutations are specific for HB, and further studies on these mutations in patients with HBs are needed to clarify this issue.

HB should be distinguished from their morphological mimickers, such as pheochromocytomas, perivascular epithelioid cell tumors (PEComas), other vascular tumors, and metastatic RCCs. In cases where vacuolated stromal cells are scant and prominent vascular structures are noted, HB may resemble capillary hem-

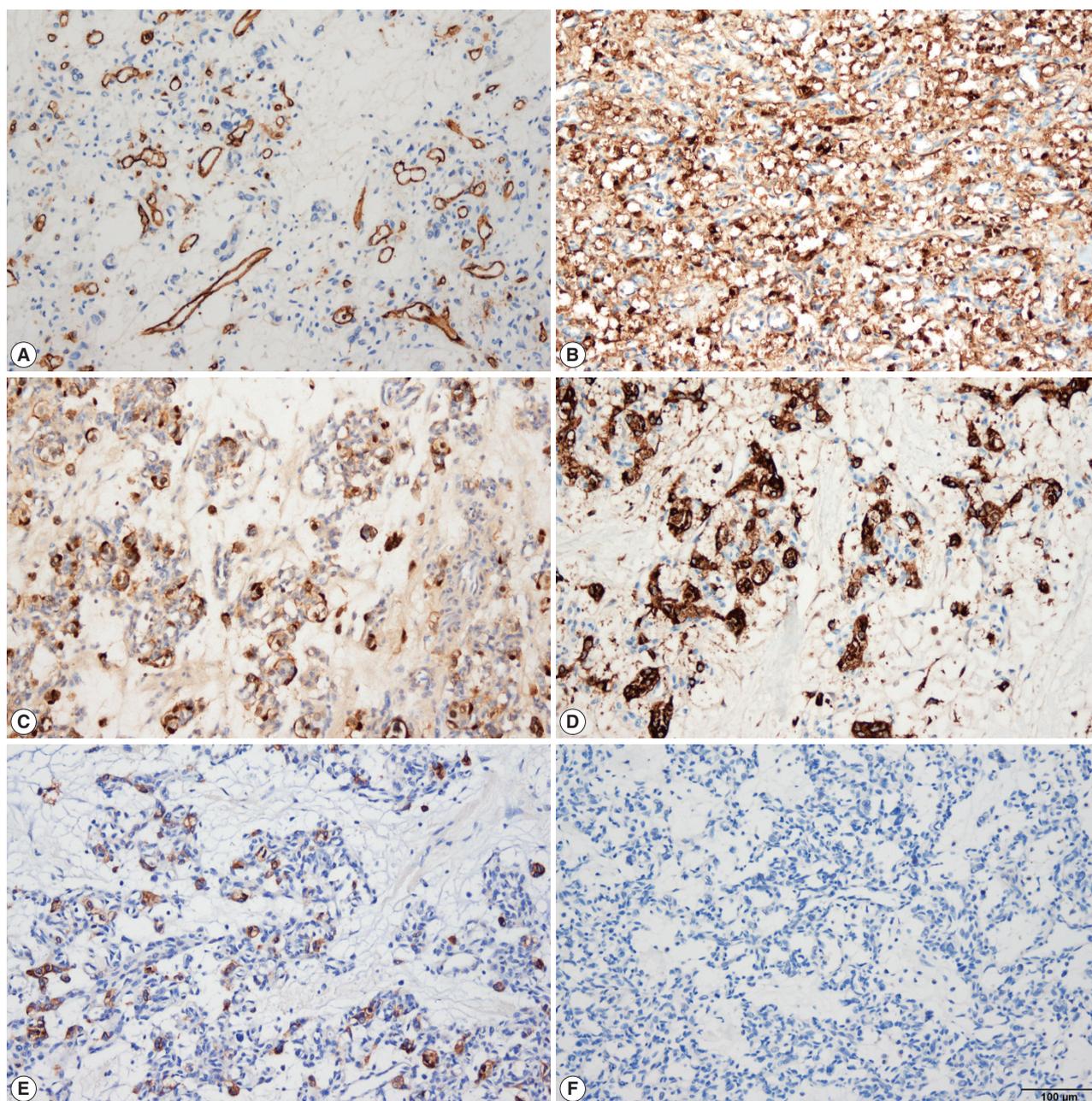


Fig. 3. Immunohistochemical staining shows that the vascular endothelial cells are positive for CD31 (A). The stromal cells are positive for NSE (B), S-100 protein (C), and synaptophysin (D). However, they are negative for chromogranin A (E) and GATA3 (F).

Table 2. The mutated genes found in the targeted sequencing

Gene symbol	RefSeq	Amino acid	Nucleotide	No. of variants/Total	VAF (%)
<i>CIC</i>	NM_015125.3	Pro911Gln	2732C>A	160/365	43.84
<i>FLCN</i>	NM_144997.5	Ser575Leu	1724C>T	165/347	47.55
<i>FLT1</i>	NM_002019.4	Ala673Val	2018C>T	348/734	47.41
<i>PARP1</i>	NM_001618.3	Val991Ala	2972T>C	297/555	53.51

RefSeq, Reference sequence; VAF, variant allele frequency.

angioma. However, capillary hemangioma lacks vacuolated or clear stromal cells, and therefore, careful examination is necessary to make a definitive diagnosis. The distinction of RCC from adrenal HB is considered as one of the most difficult differential diagnostic challenges, because RCC can spread to the adrenal gland, and their histological findings may mimic those of HB. Usually, RCC reveals a nested architecture with thin capillaries. Immunohistochemically, RCC is positive for EMA and paired-box gene 8, and negative for inhibin- α and S-100 protein. Furthermore, CA-9 is a marker for clear cell RCC, which is the most common subtype of RCC. Pheochromocytoma may arise in the adrenal medulla. Because of their anatomical location and histological findings of microvascular structure and presence of some vacuolated cells, it should be considered as a differential diagnosis of HB. However, the present case did not display a Zellballen pattern, a characteristic feature of pheochromocytomas. Other histological and immunohistochemical features were not consistent with those of pheochromocytomas. PEComa is a mesenchymal tumor with perivascular epithelioid clear cells that generally develop in the kidney, uterus, and soft tissue. Primary PEComa of the adrenal gland is extremely rare and displays a nested growth pattern of epithelioid cells. PEComa typically expresses both smooth muscle and melanocytic markers such as human melanoma black 45 and Melan-A, whereas HB does not express these markers.

In summary, adrenal HB is a rare tumor, and its unusual anatomical location and histopathological features may pose a diagnostic challenge. HB should be distinguished from their morphological mimickers, such as pheochromocytoma, PEComa, other vascular tumors, and metastatic RCC. Considering the rarity of adrenal HB, we present a case report of adrenal HB to provide recommendations for its accurate diagnosis and increased awareness of this disease.

Ethics Statement

This case report was approved by the IRB of Chonnam National University Hwasun Hospital (CNUHH-2021-240). Informed consent was obtained from the participant included in the study.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Code Availability

Not applicable.

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Conceptualization: CC. Data curation: JYK, KHL, JHC. Investigation: JYK. Methodology: YJK, KHL, HSC. Supervision: CC. Visualization: JYK. Writing—original draft: JYK. Writing—review & editing: CC, JHC. Approval of final manuscript: all authors.

Conflicts of Interest

J.H.C., a contributing editor of the *Journal of Pathology and Translational Medicine*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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