

Malignant potential of neuroendocrine microtumor of the pancreas harboring high-grade transformation: lesson learned from a patient with von Hippel-Lindau syndrome

Jongwon Lee¹, Kyung Jin Lee², Dae Wook Hwang³, Seung-Mo Hong¹

¹Department of Pathology, ²Department of Radiology and Research Institute of Radiology, ³Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Pancreatic neuroendocrine microtumor (PNEMT) is a neuroendocrine tumor (NET) < 0.5 cm in diameter, and it is considered benign. We report a PNEMT with high-grade transformation (HGT). A man in his 60s with von Hippel-Lindau syndrome underwent surgical resection of a NET. A second sub-centimeter nodule with a nodule-in-nodule pattern was discovered. The 0.4 cm outer nodule contained clear columnar cells with round nuclei and indistinct nucleoli, while the 0.1 cm inner nodule had eosinophilic cells with an increased nuclear to cytoplasmic ratio, vesicular nuclei, and prominent nucleoli. Tumor cells in the outer and inner nodules were synaptophysin and chromogranin positive. Only the inner nodule was p53 positive, while the outer nodule was exclusively positive for carbonic anhydrase 9 and vimentin. The Ki-67 labeling indices for the outer and inner nodules were 2.1% (grade 1) and 44.3% (grade 3), respectively. This nodule was determined to be a PNEMT with HGT. Our findings suggest that a PNEMT may not always be benign and can undergo HGT.

Key Words: Pancreas; Neuroendocrine; Microtumor; Immunohistochemistry; Grade; Transformation

Received: August 8, 2023 **Revised:** January 21, 2024 **Accepted:** February 9, 2024

Corresponding Author: Seung-Mo Hong, MD, PhD, Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel: +82-2-3010-4558, Fax: +82-2-472-7898, E-mail: smhong28@gmail.com

Neuroendocrine microadenomas of the pancreas are defined as small (<0.5 cm) non-functioning, well-differentiated pancreatic neuroendocrine tumors (PanNETs) [1]. They are incidentally detected during pathologic examinations because they do not cause clinical symptoms and are difficult to detect with standard imaging modalities [1,2]. PanNETs, on the other hand, are larger (≥ 0.5 cm) and are classified as malignant tumors. The metastatic potential of neuroendocrine microadenomas has been recently reported [3]. As a result, the nomenclature of neuroendocrine microadenoma was revised into pancreatic neuroendocrine microtumors (PNEMTs) in the 2022 World Health Organization (WHO) classification of neuroendocrine neoplasms due to the possibility of metastasis [4]. Here, we report the first case of an incidentally detected pancreatic PNEMT with high-grade transformation (HGT) in a patient with von Hippel-Lindau (VHL) syndrome.

CASE REPORT

Clinical features

A male patient in his 60s with clinically and genetically confirmed VHL syndrome visited for a biannual checkup. He had undergone previous surgeries, including a pylorus-preserving pancreaticoduodenectomy (PPPD) for grades 1 and 2 PanNETs and a macrocystic serous cystic neoplasm; a left partial nephrectomy for a clear cell type renal cell carcinoma and renal cysts; bilateral subtotal adrenalectomies for bilateral adrenal pheochromocytomas and a right adrenal cortical adenoma.

The patient's height and weight were within normal ranges. At the time of admission, all of his vital signs, including blood pressure, heart rate, respiratory rate, and body temperature, were within the normal range. His electrolyte levels were also within normal ranges. There were no noticeable signs of hormonal over-expression.

At this visit, 10 years after the previous pancreatic resection for the PanNETs, an abdominal computed tomography scan revealed a 2 cm well-defined hypervascular mass and two minor sub-centimeter-sized hypervascular lesions in the proximal body of the remaining body of the pancreas (Fig. 1A). The preoperative radiologic

impression of the hypervascular lesions in the pancreatic body was either recurrent PanNETs or metastatic renal cell carcinomas. There were no demonstrable tumors in the stomach, duodenum, or residual kidneys. A completion pancreatectomy was then performed.

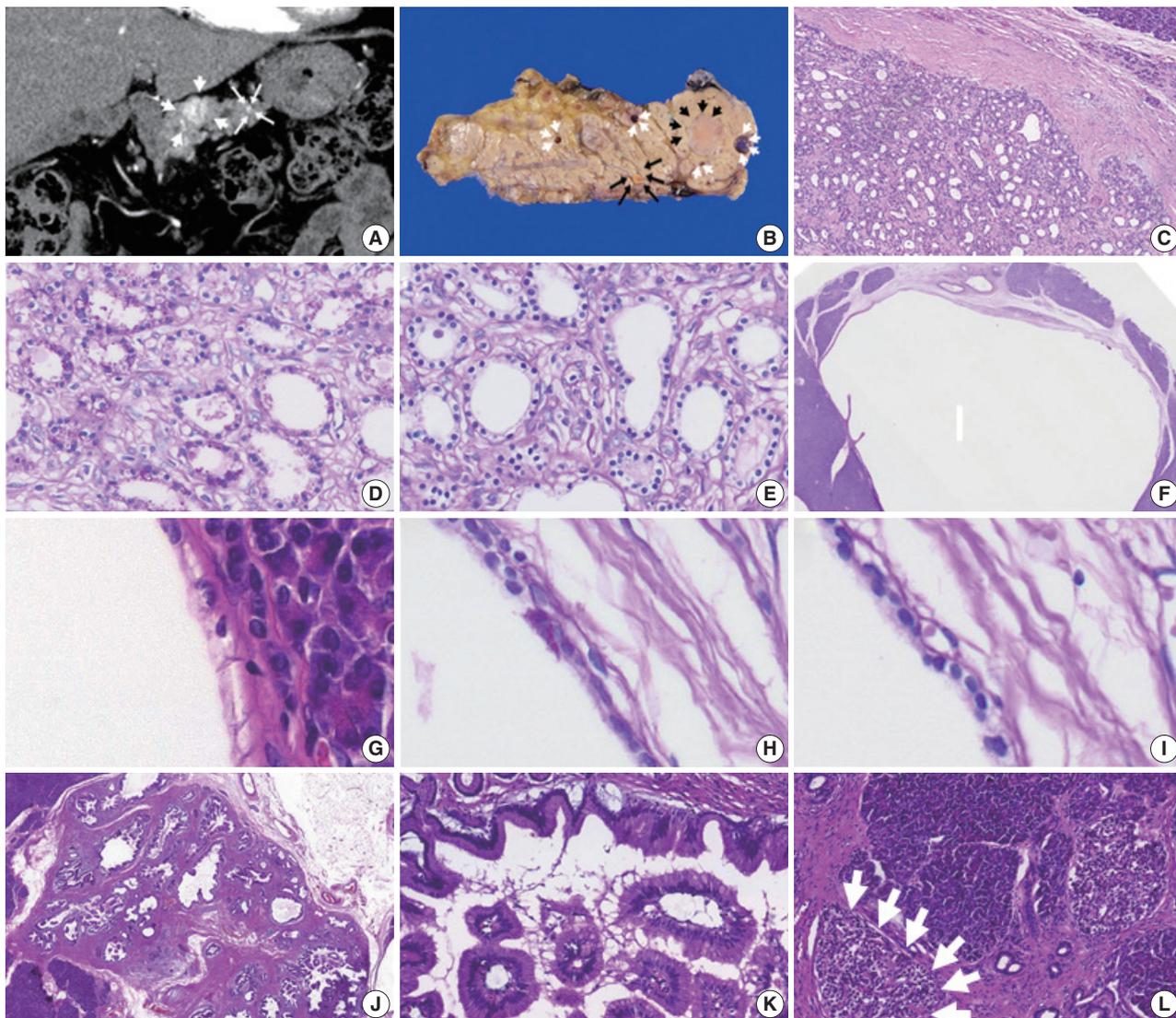


Fig. 1. (A) Computed tomography image shows a 2 cm, well-defined hypervascular mass (white arrowheads) and a sub-centimeter-sized hypervascular nodule (white arrows) in the proximal body of the remaining pancreas. (B) Completion pancreatectomy shows a 2.2 cm, well-circumscribed, yellow ovoid mass (black arrowheads), several unilocular cysts up to 0.9 cm in size (white arrowheads), and a 0.4 cm, yellowish, firm nodule (black arrows) in the remaining pancreas body. (C) Solid variant of a serous cystic neoplasm. It contains numerous small microcysts lined by monomorphic cuboidal cells with a clear cytoplasm and bland oval nuclei in a fibrotic stroma. (D) Solid variant of a serous cystic neoplasm. The clear cytoplasm of the microcystic tumor cells shows periodic acid-Schiff (PAS)-positive granules (PAS). (E) Solid variant of a serous cystic neoplasm. The PAS-positive granules are eliminated by diastase treatment (D-PAS). (F) Macrocystic variant of a serous cystic neoplasm. (G) Macrocystic variant of a serous cystic neoplasm. The cyst wall is lined by a single layer of non-mucinous cuboidal epithelial cells with a clear cytoplasm and uniform bland nuclei. (H) Macrocystic variant of a serous cystic neoplasm. The clear cytoplasm of the lining epithelial cells shows PAS-positive granules (PAS). (I) Macrocystic variant of a serous cystic neoplasm. The PAS-positive granules are diastase-sensitive (D-PAS). (J) Intraductal papillary mucinous neoplasm with low-grade dysplasia involves the main and branch ducts. (K) Intraductal papillary mucinous neoplasm with low-grade dysplasia. The papillae are lined by tall columnar mucin-containing foveolar-type epithelial cells. (L) Hypertrophic islets (white arrows).

A few solid masses and cysts were noted in the completion pancreatectomy specimen. The largest mass was a 2.2 cm, well-circumscribed, yellow ovoid mass (black arrowheads; Fig. 1B) in the pancreatic body. The solid tumor had many tiny microcysts lined by monomorphic cuboidal cells with clear cytoplasm and bland oval nuclei in fibrotic stroma (Fig. 1C). The clear cytoplasm showed periodic acid-Schiff (PAS)-positivity (Fig. 1D), which was eliminated by diastase treatment, and these findings indicated that the tumor cells contained glycogen (Fig. 1E). Despite appearing solid upon gross examination, the tumor's histologic features were consistent with a serous cystic neoplasm, and was diagnosed as a solid variant of serous cystic neoplasm.

There were five unilocular cysts up to 0.9 cm in size (white arrowheads; Fig. 1B, F) adjacent to the solid variant of a serous cystic neoplasm. The cysts were also lined by non-mucinous cuboidal epithelial cells with clear cytoplasm and uniform, bland nuclei (Fig. 1G). The clear cytoplasm showed PAS-positivity (Fig. 1H), which was eliminated with diastase treatment (Fig. 1I). Therefore, the cystic tumors were diagnosed as a macrocystic variant of a serous cystic neoplasm.

Additional gastric subtype low-grade intraductal papillary mucinous neoplasms with papillary projections involved the main and branch ductal lumens, measuring 1.6 cm in the greatest dimension (Fig. 1J). They were lined by tall columnar mucin-containing foveolar-type epithelial cells (Fig. 1K). Numerous islets with an increased size (up to 350 μm in the greatest dimension) were observed throughout the completion pancreatectomy specimen and were diagnosed as islet hyperplasia (Fig. 1L).

Finally, a 0.4 cm, yellow, well-demarcated solid tumor with

focal central red spots was observed in the pancreatic body (black arrows; Fig. 1B). The yellow tumor was cellular with a well-circumscribed nodule-in-nodule pattern (Fig. 2A). The outer nodule measured 0.4 cm in the greatest dimension and contained lightly staining monomorphic tumor cells with predominantly trabecular, focal pseudo-glandular patterns. The inner nodule was mostly circumscribed with a partial infiltration into the outer nodule (Fig. 2B). The outer nodule consisted of tumor cells with clear cytoplasm, round nuclei, and indistinct nucleoli at a higher power magnification (Fig 2C, upper half). The inner nodule, on the other hand, was 0.1 cm in size and contained darkly staining monomorphic tumor cells with a trabecular pattern (Fig 2C, lower half), and at a higher power magnification, amphophilic cytoplasm, vesicular nuclei, and prominent nucleoli were visible. Outside the tumor cells, capillaries were evenly distributed in both the inner and outer nodules. There was no geographic or spotty necrosis in either the inner or outer nodule. The mitotic counts of the tumor cells in the outer and inner nodules were 0/2 mm^2 and 10/2 mm^2 , respectively.

The immunolabeling profiles of the neoplastic cells in the inner and outer nodules differed, as shown in Table 1. Double Ki-67 and synaptophysin immunolabeling showed diffuse synaptophysin positivity in the outer nodule, and focal rim positivity in the inner nodule (Fig. 3A). The Ki-67 labeling index (Ki-67 LI) of the outer and inner nodules was 2.1% (471/22,388 cells, grade 1) and 44.3% (140/316, grade 3), respectively by manual counting after image capture. Chromogranin immunolabeling revealed diffuse positivity in the outer nodule and focal positivity in the inner nodule (Fig. 3B). Tumor cells in the inner nodule were dif-

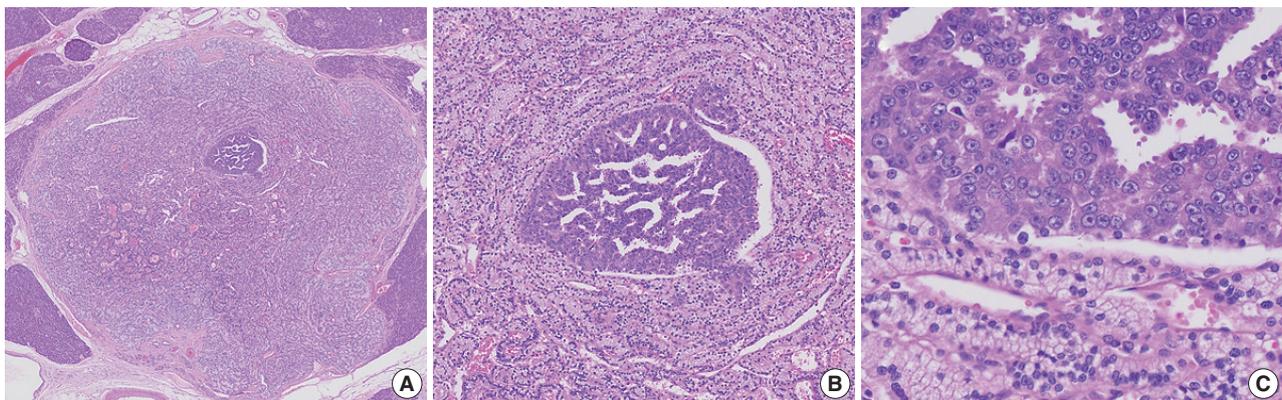


Fig. 2. Pancreatic neuroendocrine microtumor with high-grade transformation. (A) A well-circumscribed, 0.4 cm cellular tumor with a nodule-in-nodule pattern is evident. (B) The outer nodule exhibits lightly staining monomorphic tumor cells with predominantly trabecular and focal pseudo-glandular growth patterns. The inner nodule is mostly circumscribed with a partial infiltration into the outer nodule. (C) A higher power magnification view of the outer nodule (lower half) shows tumor cells with a clear cytoplasm, round nuclei, and indistinct nucleoli. The inner nodule (upper half) has darkly stained monomorphic tumor cells with a trabecular pattern. The inner nodule tumor cells have amphophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Inter-positioned capillaries are evident.

fusely immunolabeled for p53 (Fig. 3C). In contrast, p53 expression was not observed in the outer nodule. Carbonic anhydrase 9 (CA9) immunolabeling was diffusely positive in the outer nod-

Table 1. Immunohistochemical results of the pancreatic neuroendocrine microtumor

Immunohistochemistry	Outer nodule	Inner nodule
ATRX	Intact	Intact
Bcl-10	Negative	Negative
CA9	Diffuse positive	Negative
Chromogranin	Diffuse positive	Focal positive
DAXX	Intact	Intact
Glucagon	Negative	Negative
Insulin	Focal weak +	Diffuse weak +
Ki-67 LI	2.1% (471/22388)	44.3% (140/316)
MUC1	Negative	Negative
p16	Intact	Intact
p53	Wild-type	Overexpression
PAX8	Negative	Negative
Rb	Intact	Intact
Smad4	Intact, weak	Intact, strong
Synaptophysin	Diffuse positive	Focal rim positive

CA9, carbonic anhydrase 9; Ki-67 LI, Ki-67 labeling index; Rb, retinoblastoma.

ule, but was negative in the inner nodule (Fig. 3D). Smad4 immunolabeling was intact in the inner nodule but diminished in the outer nodule (Fig. 3E). Vimentin expression was observed in the outer nodule only (Fig. 3F). Tumor cells in both the inner and outer nodules expressed cytoplasmic retinoblastoma (Rb), nuclear ATRX, and DAXX immunolabelings. Both the inner and outer nodules were negative for Bcl-10. Weak insulin immunolabeling was observed diffusely in the inner nodule and focally in the outer nodule.

The final pathologic diagnosis of the 0.4 cm yellow solid tumor was a PNEMT (grade 1) with a focal HGT (grade 3). As a result, the completion pancreatectomy specimen was diagnosed as a pancreas from a VHL syndrome patient containing solid and macrocystic variants of serous cystic neoplasms, as well as a concurrent grade 1 PNEMT with a focal grade 3 transformation.

Follow-up information

The patient has no evidence of recurrence or metastasis of the PNEMTs or PanNETs 36 months after the completion pancreatectomy. However, 4 months after the pancreatectomy, his serum prostate-specific antigen level increased. A 12-core prostate

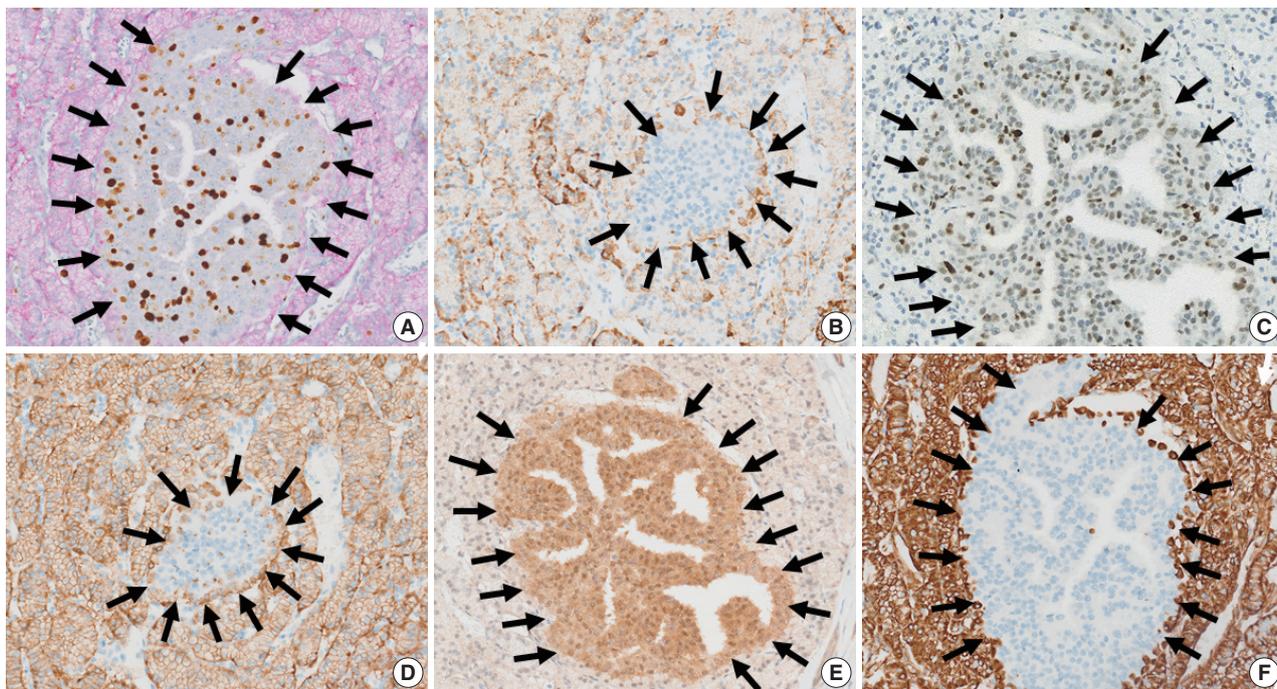


Fig. 3. Pancreatic neuroendocrine microtumor with high-grade transformation. (A) Double Ki-67 (brown) and synaptophysin (red) immunolabeling shows diffuse synaptophysin positivity in the outer nodule and focal rim positivity in the inner nodule (arrows). Double Ki-67 (brown) and synaptophysin (red). (B) Diffuse chromogranin positivity in the outer nodule and focal positivity in the inner nodule (arrows). (C) Diffuse but weak p53 labeling is only observed in the inner nodule (arrows). (D) Carbonic anhydrase 9 is diffusely positive in the outer nodule but is negative in the inner nodule (arrows). (E) Intact smad4 labeling in the inner nodule (arrows) is diminished in the outer nodule. (F) Vimentin expression is present in the outer nodule only and is absent in the inner nodule (arrows).

biopsy confirmed the presence of a prostate adenocarcinoma after several bone and lung metastases developed. He is currently receiving luteinizing hormone-releasing hormone agonist therapy.

Immunohistochemical staining

The entire surgically resected pancreas was submitted for evaluation, and 16 hematoxylin and eosin–stained sections were used. For the detection of glycogen, a PAS reaction with/without diastase treatment was used. The immunohistochemical labeling was performed at the Department of Pathology, Asan Medical Center. The primary antibodies were deployed with a Benchmark autostainer (Ventana Medical Systems, Tucson, AZ, USA) in accordance with the manufacturer's protocol. Sections were incubated at room temperature for 32 minutes in primary antibodies against ATRX (1:300, Sigma-Aldrich, St. Louis, MO, USA), Bcl-10 (1:400, Santa Cruz Biotechnology, Santa Cruz, CA, USA), CA9 (1:100, Cell Marque, Rocklin, CA, USA), chromogranin (1:200, DakoCytomation, Glostrup, Denmark), cytokeratin 19 (1:100, Cell Marque), DAXX (1:100, Sigma-Aldrich), glucagon (1:200, Cell Marque), insulin (1:1,000, Novocastra, Newcastle upon Tyne, UK), Ki-67 (1:100 DakoCytomation), MUC-1 (1:200, Novocastra), PAX-8 (1:50, Cell Marque), p16 (1:6, Santa Cruz Biotechnology), p53 (1:1,000, DakoCytomation), Rb (1:10,000, QED Bioscience, San Diego, CA, USA), smad4 (1:1,000, Abcam, Cambridge, UK), synaptophysin (1:200, Cell Marque), and vimentin (1:500, Zymed, South San Francisco, CA, USA). The sections were subsequently processed using an iView DAB detection kit with an automated immunostaining system (Benchmark XT, Ventana Medical Systems) and counterstained with hematoxylin. Double Ki-67 and synaptophysin immunolabeling was performed as previously described [5]. The PNEMT was graded by the mitotic count and Ki-67 LI according to the WHO classification [1]; grade 1, < 2 mitoses/2 mm²; Ki-67 LI < 3%; grade 2, 2–20 mitoses/2 mm² or a Ki-67 LI of 3%–20%; and grade 3, > 20 mitoses/2 mm² or a Ki-67 LI > 20%.

DISCUSSION

Pancreatic neuroendocrine microadenomas were previously considered biologically benign [1]. A recent report, however, suggested that a neuroendocrine microadenoma could be a malignant tumor because it metastasized to a peripancreatic lymph node [3]. Because of this metastatic potential, the term neuroendocrine microadenoma was changed to neuroendocrine microtumor in the 2022 WHO classification [4]. We present a rare case

of a 0.4 cm PNEMT with focal HGT, which further substantiates our proposal that PNEMT are not always benign.

The 'nodule-in-nodule' growth pattern is one of the steps in the multistep carcinogenesis model of hepatocellular carcinoma. The 'nodule-in-nodule' growth pattern manifests as a combination of an outer high-grade dysplastic nodule and an inner well-differentiated hepatocellular carcinoma, or an outer well-differentiated hepatocellular carcinoma and an inner moderately-differentiated hepatocellular carcinoma [6]. The nodule-in-nodule pattern, on the other hand, has not previously been described for PanNETs or PNEMTs.

In the current study, tumor cells in the inner nodule showed an infiltrative growth pattern. One recent study has reported a microscopic infiltrative tumor border in about 40% of surgically resected PanNETs, which was associated with higher tumor grades, larger tumors, more metastatic lymph nodes, higher American Joint Committee on Cancer stage groups, and the presence of lymphovascular and perineural invasions [7]. However, the clinicopathologic significance of a microscopic infiltrative tumor border in a PNEMT is currently unknown.

As differential diagnoses for the inner nodule, several tumors, including metastatic clear cell type renal cell carcinomas, acinar cell carcinomas, and neuroendocrine carcinomas were considered. Metastatic clear cell type renal cell carcinoma was considered as one of the differential diagnoses because the patient had VHL syndrome and previously underwent a left partial nephrectomy for clear cell type renal cell carcinoma. Although tumor cells in the outer nodule had clear cytoplasm, PAX8 immunolabeling was negative. As a result, metastatic clear cell type renal cell carcinoma was ruled out. Acinar cell carcinomas and large cell type neuroendocrine carcinomas had to be ruled out because the tumor cells in the inner nodule had amphophilic cytoplasm and prominent nucleoli. Bcl-10 cytoplasmic immunolabeling was negative in the tumor cells of the inner nodule, and acinar cell carcinoma was excluded. The tumor cells in the inner nodule showed focal and weak rim synaptophysin positivity with increased Ki-67 LI (44.3%), consistent with a grade 3 PanNET or a poorly differentiated pancreatic neuroendocrine carcinoma (PanNEC). The tumor cells of the inner nodule, however had a trabecular growth pattern with evenly interspersed capillaries, which suggested a PanNET. Furthermore, a provisional panel of immunohistochemical staining supported by the literature, including p53, p16, MUC1, and smad4, was applied to differentiate between a grade 3 PanNET and a PanNEC [8], and the panel's results favored a grade 3 PanNET over a PanNEC in the current case. In addition, chromogranin, CA9, and vimentin ex-

pression patterns differed between the inner and outer nodules. There was focal chromogranin labeling but no CA9 or vimentin immunolabeling tumor cells in the inner nodule. The outer nodule, conversely, showed diffuse chromogranin, CA9, and vimentin expression. Islets of Langerhans are vimentin-negative but are immunolabeled for CA9 [9]. CA9 and vimentin expressions were found in only 9% (2/23 cases) and 30% (7/23 cases) of PNEMTs, respectively, in a previous study [9]. In the same study, CA9 expression in PanNETs was associated with aggressive behavior and poor survival [9]. Vimentin expression has not been found to be related to the clinical behavior of PanNETs [9]. This may be evidence that CA9 participates in an early PanNET tumorigenesis stage, specifically, the microtumor stage, and is linked to a worse clinical outcome.

PNEMTs can appear sporadically or as a part of hereditary syndromes [10–14]. The prevalence of PNEMTs varies with the amount of pancreatic tissue obtained (0.4%–10%) [15]. One previous autopsy study reported that the incidence of PNEMT was 1.6% (12/738) when three random histologic sections were submitted, but the incidence increased up to 10% (6/60) when entire pancreas tissues were submitted [2]. The most commonly reported grades of PNEMTs were grade 1, regardless of whether they were sporadic or syndromic in origin [12,16]. Only a few cases of grade 2 PNEMTs have previously been reported in the English-language literature [16,17]. De Wilde and colleagues observed one case of grade 2 microtumor out of 47 PNEMTs of the pancreas in patients with multiple endocrine neoplasia type 1 (MEN1) syndrome [17]. Furthermore, Okawa and colleagues reported one case of grade 2 PNEMT from a patient suspected of MEN1 syndrome among 23 PNEMTs evaluated for Ki67 LI (4%, 1 of 23) [16]. However, to the best of our knowledge, no PNEMT with histology greater than grade 2 has been reported in a patient with VHL syndrome in the English literature. The current case may be the first PNEMT containing distinct grade 1 and grade 3 areas with a nodule-in-nodule pattern. We did not define the area distinctions solely on the basis of KI-67 LI. Intra-tumoral differences in Ki-67 LI in large tumors, including PanNETs, could be interpreted as tumor heterogeneity [18]. However, distinct synaptophysin immunohistochemical staining patterns in inner and outer nodules, as seen in this case, cannot be explained by tumor heterogeneity alone.

PanNETs are found in approximately 11% to 17% of VHL syndrome patients and are typically multiple tumors at the time of detection [19]. In addition to multiple PanNETs, patients with VHL syndrome may develop a number of precursor lesions, including PNEMTs [20]. Several histologic evidences of VHL

syndrome were found in both the patient's previous PPPD and the completion pancreatectomy specimens, including three PanNETs, one with grade 2 and two with grade 1 pathology, a PNEMT with HGT, multiple macrocystic serous cystic neoplasms, and a solid serous cystic neoplasm. Multiple neuroendocrine tumors that recur are uncommon in non-syndromic settings [19,21]. The current PanNETs have a clear cytoplasm, which has previously been reported as a feature of VHL syndrome [20]. Furthermore, the findings of multiple macrocystic serous cystic neoplasms in the PPPD and the completion pancreatectomy specimens are consistent with VHL syndrome involvement.

As for study limitations, our study faced constraints in utilizing hypoxia-inducible factor 1 α (HIF1 α) and glucose transporter 1 (GLUT1) immunolabeling. The disappearance of the inner nodule in microtumor precluded the evaluation of the transformed area in the HIF1 α and GLUT1 immunolabeling sections, impeding our ability to investigate these markers comprehensively.

In summary, this case was diagnosed as a PNEMT with HGT. Our findings suggest that PNEMTs may not be benign tumors and can undergo HGT, as exemplified by the current patient with VHL syndrome.

Ethics Statement

This case was deemed exempt from informed consent by the Asan Medical Center institutional review board (IRB #2022-0228).

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.

ORCID

Jongwon Lee	https://orcid.org/0000-0003-3057-7874
Kyung Jin Lee	https://orcid.org/0000-0003-4689-5287
Dae Wook Hwang	https://orcid.org/0000-0002-1749-038X
Seung-Mo Hong	https://orcid.org/0000-0002-8888-6007

Author Contributions

Conceptualization: JL, SMH. Data curation: JL, KJL, DWH. Formal analysis: JL, KJL. Investigation: JL, SMH. Methodology: JL, SMH. Supervision: SMH. Validation: JL, SMH. Writing—original draft: JL, SMH. Writing—review & editing: JL, KJL, SMH. Approval of final manuscript: all authors.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

Funding Statement

No funding to declare.

References

1. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; 76: 182-8.
2. Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci* 1991; 36: 933-42.
3. Kwon JH, Kim HJ, Park DH, et al. Incidentally detected pancreatic neuroendocrine microadenoma with lymph node metastasis. *Virchows Arch* 2018; 473: 649-53.
4. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol* 2022; 33: 115-54.
5. Ahn B, Jung JK, Jung H, et al. Double Ki-67 and synaptophysin labeling in pancreatic neuroendocrine tumor biopsies. *Pancreatology* 2022; 22: 427-34.
6. Kojiro M. 'Nodule-in-nodule' appearance in hepatocellular carcinoma: its significance as a morphologic marker of dedifferentiation. *Intervirolgy* 2004; 47: 179-83.
7. Ahn B, Kim JY, Hong SM. Combined infiltrative macroscopic growth pattern and infiltrative microscopic tumor border status is a novel surrogate marker of poor prognosis in patients with pancreatic neuroendocrine tumor. *Arch Pathol Lab Med* 2023; 147: 100-16.
8. Kim H, An S, Lee K, et al. Pancreatic high-grade neuroendocrine neoplasms in the Korean population: a multicenter study. *Cancer Res Treat* 2020; 52: 263-76.
9. Kim JY, Lee SH, An S, et al. Carbonic anhydrase 9 expression in well-differentiated pancreatic neuroendocrine neoplasms might be associated with aggressive behavior and poor survival. *Virchows Arch* 2018; 472: 739-48.
10. Chetty R, Kennedy M, Ezzat S, Asa SL. Pancreatic endocrine pathology in von Hippel-Lindau disease: an expanding spectrum of lesions. *Endocr Pathol* 2004; 15: 141-8.
11. Chetty R, Ezzat S, Asa SL. Microadenomatosis of the pancreas in von Hippel-Lindau disease. *Am J Surg Pathol* 2006; 30: 1630.
12. Anlauf M, Schlenger R, Perren A, et al. Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. *Am J Surg Pathol* 2006; 30: 560-74.
13. Perigny M, Hammel P, Corcos O, et al. Pancreatic endocrine microadenomatosis in patients with von Hippel-Lindau disease: characterization by VHL/HIF pathway proteins expression. *Am J Surg Pathol* 2009; 33: 739-48.
14. Akatsu T, Aiura K, Ito Y, Ueda M, Kameyama K, Kitajima M. A novel Von Hippel-Lindau case with germline mutation at codon 167 (CGG to TGG) having endocrine microadenomatosis of the pancreas. *Dig Dis Sci* 2007; 52: 3145-8.
15. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. Geneva: World Health Organization, 2010.
16. Okawa Y, Tsuchikawa T, Hatanaka KC, et al. Clinical features of pancreatic neuroendocrine microadenoma: a single-center experience and literature review. *Pancreas* 2022; 51: 338-44.
17. de Wilde RF, Heaphy CM, Maitra A, et al. Loss of ATRX or DAXX expression and concomitant acquisition of the alternative lengthening of telomeres phenotype are late events in a small subset of MEN-1 syndrome pancreatic neuroendocrine tumors. *Mod Pathol* 2012; 25: 1033-9.
18. Hwang HS, Kim Y, An S, et al. Grading by the Ki-67 labeling index of endoscopic ultrasound-guided fine needle aspiration biopsy specimens of pancreatic neuroendocrine tumors can be underestimated. *Pancreas* 2018; 47: 1296-303.
19. Lubensky IA, Pack S, Ault D, et al. Multiple neuroendocrine tumors of the pancreas in von Hippel-Lindau disease patients: histopathological and molecular genetic analysis. *Am J Pathol* 1998; 153: 223-31.
20. Cassol C, Mete O. Endocrine manifestations of von Hippel-Lindau disease. *Arch Pathol Lab Med* 2015; 139: 263-8.
21. Hammel PR, Vilgrain V, Terris B, et al. Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. *Gastroenterology* 2000; 119: 1087-95.