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CASE REPORT

Surgical resection of double advanced pancreatic neuroendocrine tumors with multiple renal cell carcinoma associated with von Hippel–Lindau disease

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Abstract

Von Hippel–Lindau (VHL) disease, an autosomal dominant genetic disorder caused by a germline mutation, is associated with non-functional and slow-growing pancreatic neuroendocrine tumor (PNET) and kidney cancer. We describe the case of a 46 year-old man with a 35 mm mass in the pancreatic head causing stricture of the bile duct and main pancreatic duct, a 55 mm mass in the pancreatic tail causing obstruction of the splenic vein (SV), and multiple masses of > 36 mm on both kidneys. We performed a two-stage resection. First, a total pancreatectomy with superior mesenteric vein (SMV) resection and reconstruction and retroperitoneoscopic right partial nephrectomy (NP) for five lesions was performed, followed by retroperitoneoscopic left partial NP of the five lesions 6 months later. Postoperative histopathological examination revealed NET G2 in the pancreatic head with SMV invasion and somatostatin receptor type 2A (SSTR2A) positivity, NET G2 in the pancreatic tail showed SV invasion and negative SSTR2A, and multiple clear cell renal cell carcinomas (RCC) were also noted. Multiple liver recurrences occurred 22 months after primary surgery. The patient remains alive 41 months after primary surgery. Kidney cancer generally determines VHL prognosis; however, we experienced dual-advanced PNETs with a more defined prognosis than multiple RCC associated with VHL.

Keywords Pancreatic neuroendocrine tumor · Von Hippel–Lindau disease · Total pancreatectomy · Portal vein resection · Surgical resection

Introduction

Von Hippel–Lindau disease (VHL) is an autosomal dominant genetic disorder caused by a germline mutation in a tumor suppressor gene, which is associated with various diseases, such as retinal hemangioma, central nervous system hemangioblastoma, pancreatic neuroendocrine tumor (PNET), kidney cancer, adrenal pheochromocytoma, and epididymal pustular adenoma [1]. PNET occurs in 8–17% of patients with VHL disease [2]. Most PNETs associated with VHL are non-functional and asymptomatic [3, 4], and are often detected earlier than sporadic non-functional PNETs, with 11–20% of cases presenting distant metastases at the first visit [5]. Regardless of the presence of VHL disease, PNET progresses slowly and has a relatively good prognosis [3]. Therefore, very few cases occur in which PNETs must be treated before other lesions of VHL disease, and thus, few reports on the resection of advanced PNETs are available in the literature.

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Herein, we describe the case of a patient who underwent surgical resection of two advanced PNETs associated with VHL, suggesting heterogeneity, combined with multiple renal cell carcinoma (RCC), which may indicate a more defined prognosis than resected multiple RCC.

Case report

A 46 year-old man was referred to our hospital by his primary care physician for further investigation due to abdominal pain. He had a history of diabetes and had undergone surgery for parietal lobe hemangioblastoma at 30 years of age. His younger brother had VHL disease and had been treated for spinal hemangioblastoma, retinal hemangioblastoma, PNET, and adrenal gland tumors. His mother died of brain disease with no detailed history available. Although the patient knew that there was a high possibility that he would have VHL disease, he had voluntarily stopped visiting his previous doctor and did not undergo regular screenings. He was diagnosed with VHL disease based on a history of parietal lobe hemangioblastoma and a family history of VHL disease. Laboratory examinations revealed increased serum levels of hemoglobin A1c (7.8%, normal range; 4.9–6.0%) and normal levels of amylase, lipase, and hepatobiliary systemic enzymes. Tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19–9, S-pancreas antigen-1, Duke pancreatic monoclonal antigen type 2, and neuron-specific enolase, were also within normal limits, and there were no abnormalities in the serum levels of gastrointestinal and pancreatic hormones including growth factor hormone (0.70 ng/mL, normal range; 0–2.47 ng/mL), serum gastrin (96 pg/mL, normal range; 0–200 pg/mL), fasting immunoreactive insulin (6.2 μU/mL, normal range; 5–15 μU/mL), or C-peptide immunoreactivity (1.19 ng/mL; normal range; 0.61–2.09 ng/mL). Initial multidetector-enhanced computed tomography (CT) revealed a 35-mm irregularly enhanced mass with less than 180° contact with the superior mesenteric vein (SMV) in the pancreatic head, causing stricture of the bile duct and stricture and main pancreatic duct (Fig. 1a); a 55 mm irregularly enhanced mass in the pancreatic tail causing obstruction of the splenic vein (SV) and formation of collateral circulation (Fig. 1b); localized dilatation of the main pancreatic duct in the pancreatic body (Fig. 1c); and multiple enhanced masses up to 36 mm in size in both kidneys (Fig. 1d). Esophagogastroduodenoscopy revealed no abnormalities. Colonoscopy showed a sigmoid diverticulum. Positron emission tomography (PET)-CT revealed tumors in the head of the pancreas (standardized uptake value [SUV] max, 6.14) (Fig. 2a) and tail (SUV max, 2.88) (Fig. 2b) with increased fluorodeoxyglucose (FDG) uptake. Somatostatin receptor scintigraphy (SRS) indicated accumulation of radioactivity in the tumor located in the pancreatic head (Fig. 2c), which was absent in the tumor in the pancreatic tail (Fig. 2d). We performed endoscopic retrograde cholangiopancreatography (ERCP) to evaluate the presence or absence of bile duct stricture and the possibility of bile duct invasion due to the pancreatic head tumor. Furthermore, ERCP allowed detailed pancreatic duct examination and pancreatic fluid cytology analysis based on initial multidetector-enhanced CT images revealing localized dilatation of the main pancreatic duct in the pancreatic body (Fig. 1c). ERCP revealed a stricture of the common distal bile duct (Fig. 3a) and a stricture of the main pancreatic duct in the

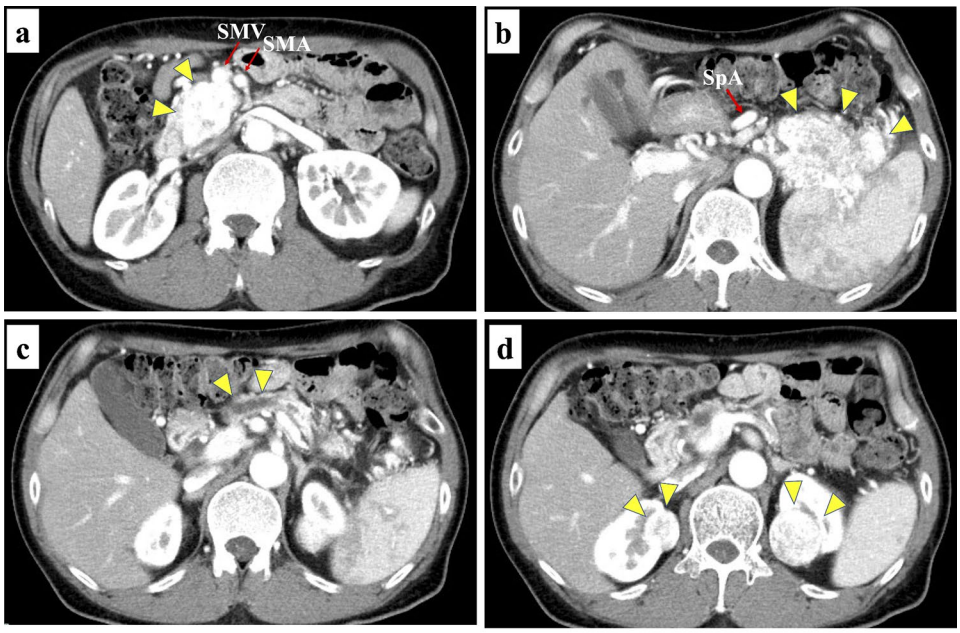

Fig. 1 Initial multidetector computed tomography images. **a** A 35 mm mass visible in the pancreatic head (yellow arrowhead). **b** A 55 mm mass visible in the pancreatic tail (yellow arrowhead). **c** Dilatation of the main pancreatic duct in the pancreatic body (yellow arrowhead). **d** Multiple masses up to 36 mm in size visible on both kidney (yellow arrowhead) (colour figure online)

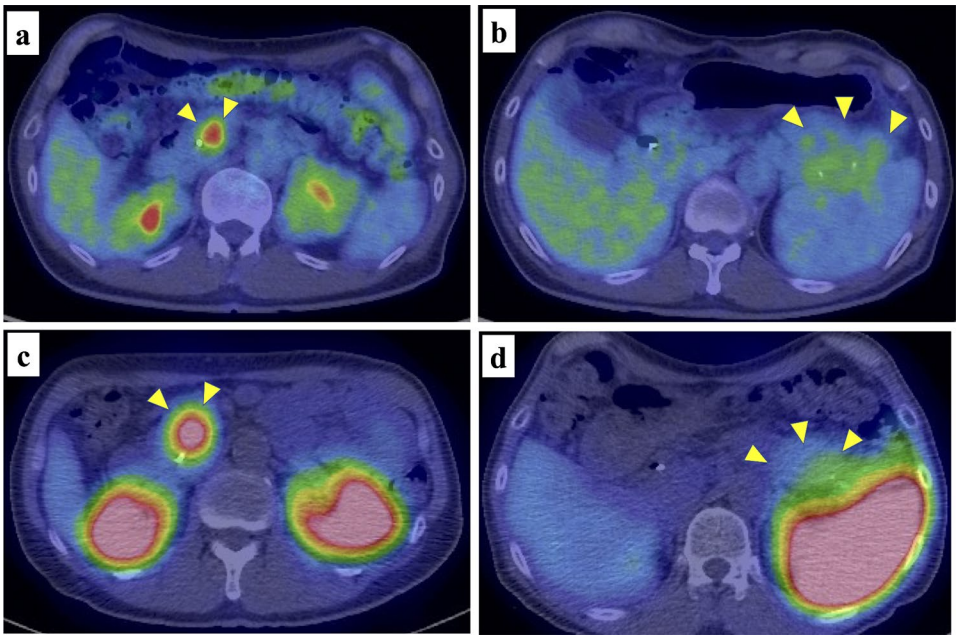

Fig. 2 **a** Preoperative positron emission tomography-computed tomography images. The tumor in the pancreatic head showing increased FDG uptake (SUV 6.14) (yellow arrowhead). **b** The tumor in the pancreatic tail showing increased FDG uptake (SUV 2.88) (yellow arrowhead). **c** Preoperative somatostatin receptor scintigraphy images. The tumor in the pancreatic head showing accumulation of radioactivity (yellow arrowhead). **d** The tumor in the pancreatic tail with no accumulation of radioactivity (yellow arrowhead). *FDG* fluorodeoxyglucose *SUV* standardized uptake value (colour figure online)

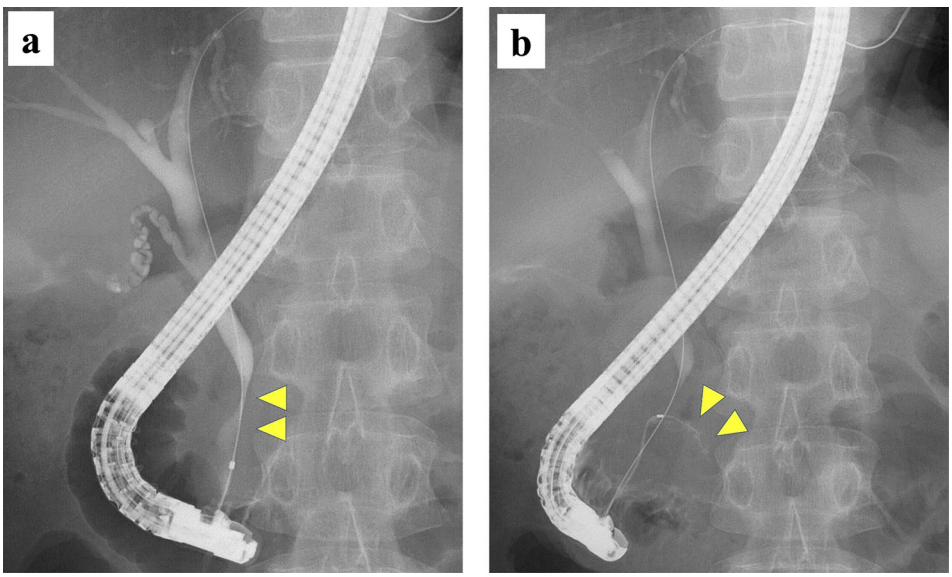

Fig.3 Preoperative endoscopic retrograde cholangiopancreatography images. **a** Distal common bile duct stricture (yellow arrowhead). **b** Main pancreatic duct stricture in the pancreatic head (yellow arrowhead) (colour figure online)

pancreatic head (Fig. 3b). Cytological examination of the pancreatic fluid obtained by ERCP was unremarkable for malignancy. We performed endoscopic ultrasonography-guided fine-needle aspiration of the pancreatic tumors. The resulting histological examination showed pancreatic tissue with no malignant findings in the pancreatic head tumor, whereas the tumor in the pancreatic tail was suspected to be a NET, which was positive for synaptophysin, chromogranin A, and Ki-67 staining observed in 1% of tumor cells. The preoperative diagnosis was NET in the head and tail and multiple RCC. Considering the clinical findings caused by the PNETs and tumor size, we performed surgical resection of the two PNETs. Furthermore, multiple RCCs > 2 cm were detected in both kidneys, which led to their resection in two-stages. Although a total pancreatectomy was avoided and the pancreatic body was preserved, the procedure was complex. The length of the remaining pancreas was approximately 2 cm; therefore, it is considered to be of little significance for the preservation of pancreatic function. We first performed total pancreatectomy (TP) with superior mesenteric vein (SMV) resection and reconstruction with end-to-end anastomosis and retroperitoneoscopic right partial nephrectomy (NP) for the five lesions having a tumor diameter > 2 cm. Six months after the primary surgery, the patient underwent retroperitoneoscopic left partial NP for five lesions with a tumor diameter > 2 cm.

The gross and histopathological findings of the resected specimen revealed a well-differentiated PNET in the pancreatic head measuring 36×35 mm with SMV and duodenal invasion (Fig. 4a, 4c), a well-differentiated PNET in the pancreatic tail measuring 74×51 mm with SV and invasion of the main pancreatic duct (Fig. 4b, 4d), seven clear cell RCC lesions with nuclear atypia G2, measuring a maximum size of 35 mm to a minimum size of 5 mm, and three simple cysts. No lymph node metastases were observed. Immunostaining of the resected sample showed that the tumor cells in the pancreatic head stained positive for synaptophysin (Fig. 5a), focally positive for chromogranin A (Fig. 5b), and partially positive for somatostatin receptor type 2A (SSTR2A) (Volante score 2 [6]) (Fig. 5c). The Ki-67 labeling index was 15% and the mitotic count was 1/50 high-power fields. The tumor cells in the pancreatic tail stained positive for synaptophysin (Fig. 5d), some were positive for chromogranin A (Fig. 5e), and negative for SSTR2A (Volante score 0) (Fig. 5f); the Ki-67 labeling index was 10% and the mitotic count was 0/50 high-power fields. Pathological diagnosis was NET G2 in the pancreatic head (T3N0M0, stage II) and NET G2 in the pancreatic tail (T3N0M0, stage II) according to the 8th edition of the Union for International Cancer Control tumor-node-metastasis classification [7].

Approximately 22 months after primary surgery, we confirmed multiple liver recurrence based on multidetector-enhanced CT imaging (Fig. 6a) and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced liver magnetic resonance imaging (EOB-MRI) (Fig. 6b–d). We first administered everolimus [8]; however, adverse events, such as fatigue and loss of appetite, occurred. Therefore, we consulted with the patient and switched treatment to lanreotide [9, 10], which was administered at a dose of (120 mg) every 4 weeks. The patient is currently alive more than 41 months after primary surgery.

Discussion

In this report, we describe a rare presentation of two advanced PNETs lesions with SMV and SV invasion in the pancreas, and with multiple RCC associated with VHL disease, in a 46 year-old man. We performed TP with SMV resection, reconstruction, and retroperitoneoscopic right partial NP for five larger lesions. Six months after the primary surgery, the patient underwent left NP partial nephrectomy for an additional five lesions.

PNETs are generally slow-growing tumors, regardless of the presence or absence of VHL disease. PNET associated with VHL causes death in 0.3% of all patients with VHL, and considering the incidence of PNET associated with VHL is 1.9% overall, the prognosis is relatively good

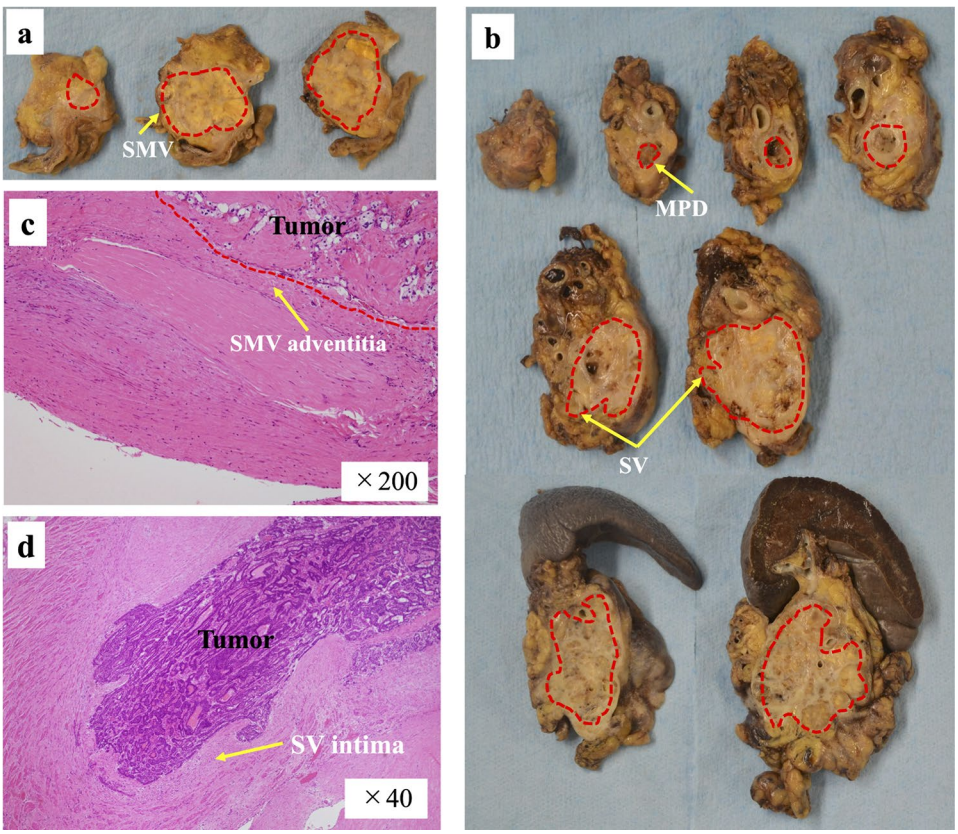

Fig. 4 Gross and histopathologic findings of the resected specimen. (**a**) Tumor in the pancreatic head measuring 36×35 mm with SMV invasion (red dotted line). **b** Tumor in the pancreatic tail measuring 74×51 mm with SV invasion and main pancreatic duct invasion (red dotted line). **c** Tumor in the pancreatic head with SMV invasion (red dotted line) (×200). **d** Tumor in the pancreatic tail with SV invasion (×40). *SMV* superior mesenteric vein, *SV* splenic vein (colour figure online)

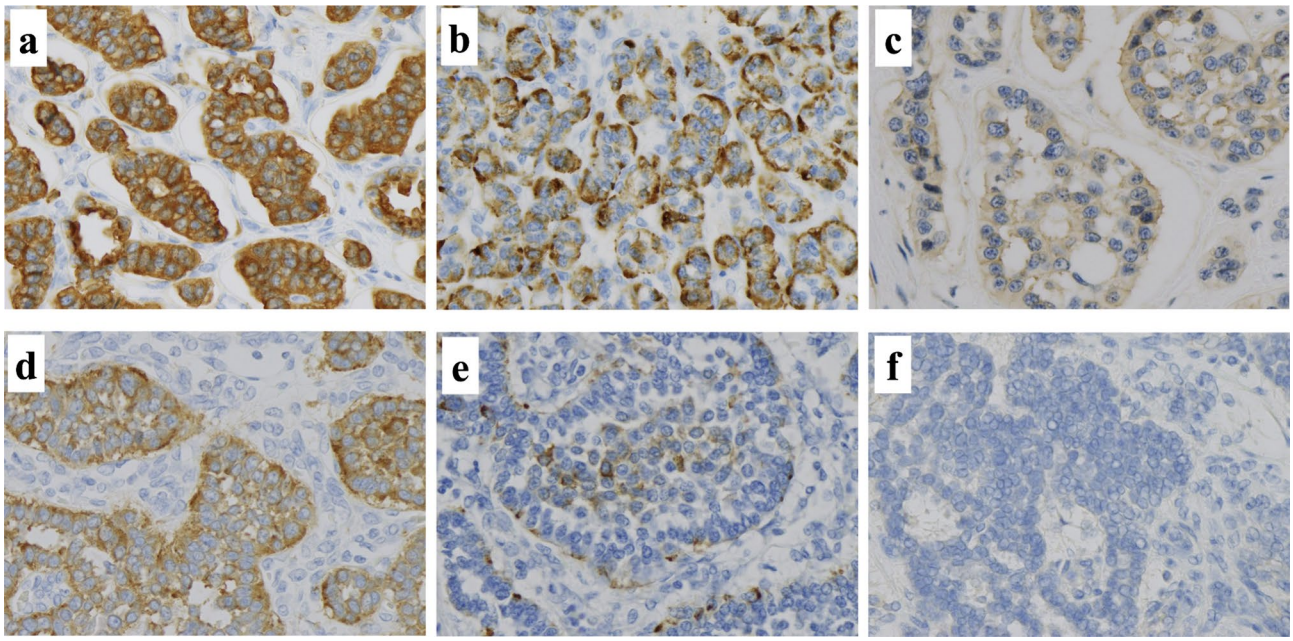

Fig. 5 Immunostaining findings of the resected specimen (×400). The tumor cells in the pancreatic head staining **a** positive for synaptophysin, **b** focally positive for chromogranin A, and **c** partially positive for SSTR2A. The tumor cells in the pancreatic tail staining **d** positive for synaptophysin, **e** a few positive cells for chromogranin A, and **f** negative for SSTR2A. *SSTR2A* somatostatin receptor type 2A

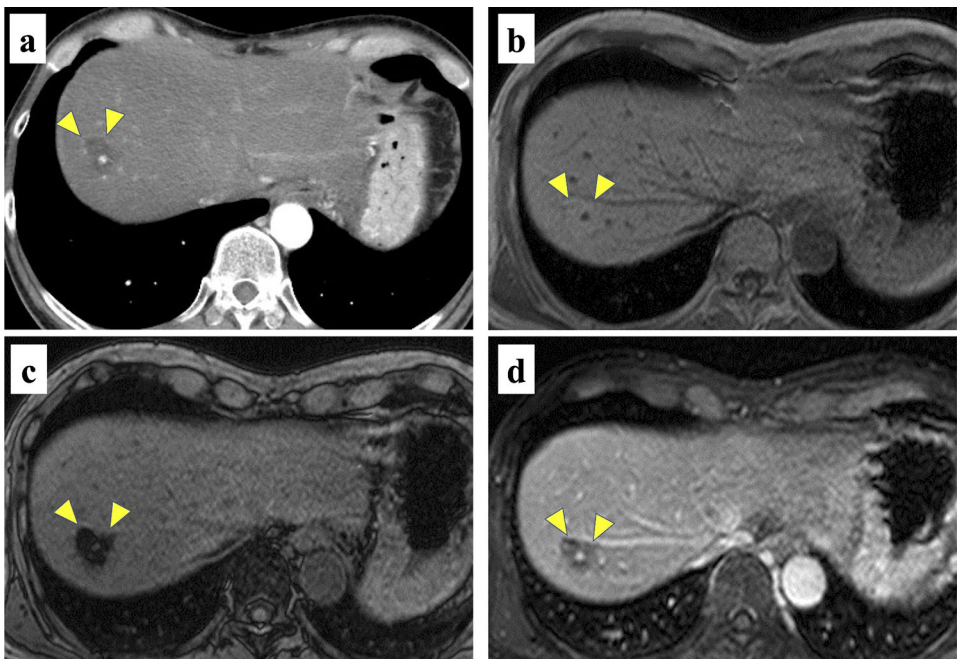

Fig. 6 **a** Multidetector computed tomography images 22 months after primary surgery. Liver tumors with early enhancement (yellow arrowhead). **b** Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced liver magnetic resonance images 22 months after primary surgery. Chemical shift imaging with in-phase imaging showed peritumoral steatosis (yellow arrowhead) **c** Chemical shift imaging with out-phase imaging showed peritumoral steatosis (yellow arrowhead). **d** Liver tumor with early enhancement at the early phase (yellow arrowhead) (colour figure online)

[3]. The presence of two advanced PNETs with vascular invasion was rare in our case. PNETs occurred in multiple liver recurrences, but residual RCCs did not increase with tumor size; thus, the PNETs likely determined prognosis. Maeda et al. [11] reported a total pancreatectomy combined with portal vein resection for multiple PNETs with SMV invasion. In their case, one of the multiple PNETs showed vascular invasion. PNET-associated VHL often occurs or recurs as multiple tumors and can be complicated by RCC. Multiple surgical resections are often required; therefore, careful decision-making is needed for surgical planning and resection of PNET [1]. Blansfield et al. [3] identified three

prognostic factors for PNET associated with VHL: maximum tumor size ≧ 3 cm, mutations in exon 3 of the VHL gene, and tumor doubling time 500 days. In addition, distant metastasis did not occur in any patients not exhibiting any of these three prognostic factors or in those positive for only one factor; however, distant metastasis occurred in 33% of patients with two factors and in 67% of patients with three factors. The authors did not perform genetic investigations for all patients with VHL, despite the detection rate for mutations in the VHL gene has been reported to be approximately 80% [12]. Therefore, it may be controversial to include results from genetic research in the surveillance of VHL disease. In our case, we did not investigate mutations in exon 3 of the VHL gene and we did not measure the tumor doubling time. Regarding the malignant potential of PNETs, Yang et al. [13] indicated that overall survival decreased in patients with an ill-defined tumor margin, irregular shape, poor differentiation, grade 3 disease, non-functional status, abnormal tumor marker levels, invasion into nearby tissues, lymph node and liver metastases, and lower oxygen enhancement ratio. In addition, Nanno et al. [14] reported that main pancreatic duct involvement in well-differentiated neuroendocrine tumors was an independent poor prognostic factor. Considering the tumor size ≥ 3 cm and the clinical findings in our patient, including stricture of the bile duct, stricture of the main pancreatic duct, and obstruction of the splenic vein, which were potential indicators of the malignant potential of PNET, conservatively monitoring the PNETs may have led to the progression of PNETs and unresectable PNETs; thus, we decided to prioritize treatment for PNETs and perform upfront surgery without monitoring.

According to previous reports [15–18], simultaneous surgical resection of PNET and RCC associated with VHL may be a suitable treatment option for selected patients (Table 1). In these reports, surgical interventions consisting of pancreatoduodenectomy and right nephrectomy were performed in two patients and distal pancreatectomy and right nephrectomy was performed in one patient; details were unknown in one patient. In our case, retroperitoneoscopic right partial NP of three lesions was performed and the prerenal fascia was maintained, followed by TP with SMV resection. TP was performed in the retropancreatic fascia layer rather than in the radical antegrade modular pancreatosplenectomy layer [19]. Six months later, partial retroperitoneoscopic left NP was performed for five lesions. Of the multiple RCC lesions, we targeted tumors > 2 cm in size [1]; thus, residual RCCs was present.

VHL is a hereditary syndrome characterized by a predisposition to various multicentric diseases, including retinal angiomas, hemangioblastomas in the central nervous system, RCCs, pheochromocytomas, and islet cell tumors of the pancreas [20]. In our case, two advanced PNET lesions exhibited a slight difference on contrast medium with initial multidetector-enhanced CT and also exhibited different findings in the preoperative PET-CT and SRS images and in immunostaining findings of the resected specimen, demonstrating multicentric development. Glucose metabolism does not necessarily increase in well-differentiated NETs, and the positive rate of PET-CT is low. Panagiotidis et al. [21] reported that the rate of FDG-PET positivity was 3% in NET G1, 25% in NET G2, and 39% in NET G3, respectively. Conversely, PET-CT may be useful to detect metastasis and tumor recurrence with high proliferative potential [22]. SRS is dependent on somatostatin receptors and has a sensitivity of 52% and a specificity of 93% [23]. SSTR2A positivity was significantly higher in NET G1 and NET G2 tumors than in neuroendocrine carcinoma [24]. SSTR2A expression is an independent prognostic factor for survival in PNETs [25]. Moreover, lanreotide, a somatostatin analog, is a synthetic peptide with high affinity for SSTR2 and SSTR5 [9]; thus, the evaluation of SSTR2A status in histopathologic findings may predict the response of PNETs to somatostatin analogs.

Table 1 Reported cases of simultaneous surgical resection for PNET and RCC associated with VHL

Author [Ref]	Age	Sex	Preoperative diagnosis	PNET size (mm)	Location of PNET	Operation method	PNET grade	Pathological tumor findings	Postoperative survival
Osawa et al. [15]	43	F	PNET or RCC-meta	30	Head	PD + Rt. NP	Highly differentiating endocrine cancer	v2, ly2, ne2	Alive (3 months)
Addeo et al. [16]	27	F	Pancreatic neoplasm	Not described	Head	PD + Rt. partial NP	G1	No vascular/neural invasion	Alive (6 months)
Matsubayashi et al. [17]	79	M	RCC-meta	15	Tail	Laparotomy (details unknown)	G1	T3	Alive (4 years)
Woo et al. [18]	47	F	Not described	Not described	Tail	DP + Rt. NP	Not described	Not described	Not described

PNET pancreatic neuroendocrine tumor, *RCC*, renal cell carcinoma, *VHL* Von Hippel–Lindau, *meta* metastasis, *PD* pancreatoduodenectomy, *Rt.* right, *NP* nephrectomy, *DP* distal pancreatectomy, *v* venous invasion, *ly* lymphatic invasion, *ne* neural invasion

Twenty-two months after primary surgery, multiple liver recurrences occurred. Lesions were confirmed based on multidetector-enhanced CT imaging that showed multiple liver tumors with early enhancement (Fig. 6a) and EOB-MRI that indicated multiple liver tumors with early enhancement and peri-tumoral steatosis [26, 27] (Fig. 6b–d). Disease control in unresectable PNET may require systemic chemotherapy, including lanreotide [9, 10], everolimus [8], sunitinib [28], and streptozocin [29, 30]. Considering the relatively high Ki-67 index of the surgical specimen and the large tumor volume, we first administered everolimus; however, adverse events, such as fatigue and loss of appetite, occurred. Therefore, we switched to lanreotide 120 mg every four weeks to control the disease. Although peptide receptor radionuclide therapy, targeting NET patients with high SSTR expression [31], has not been implemented at our hospital, it may be a treatment option.

In conclusion, our patient presented with double advanced PNET lesions with a potentially more defined prognosis compared to the occurrence of multiple RCC associated with VHL. Our patient underwent TP with SMV resection and reconstruction and two retroperitoneoscopic partial NPs. In general, PNETs are slowly growing tumors, and in very few situations, treatment for PNETs must be given priority over surgery, including for other diseases such as RCCs. Surgical resection discussed in our case report may not necessarily represent the definitive solution. However, it may be a treatment option for advanced PNETs to ensure better disease control.

Author contributions Study conception and design: Yoshiyuki Shibata, Takeshi Sudo. Acquisition of data: Yoshiyuki Shibata, Takeshi Sudo, Sho Tazuma, Takashi Onoe, Atsushi Yamaguchi, Masanobu Shigeta, Kazuya Kuraoka, Rie Yamamoto, Hirotaka Tashiro. Analysis and interpretation of data: Yoshiyuki Shibata, Takeshi Sudo, Kazuya Kuraoka, Rie Yamamoto. Drafting of manuscript: Yoshiyuki Shibata, Takeshi Sudo. Critical revision of manuscript: Yoshiyuki Shibata, Takeshi Sudo, Shinya Takahashi.

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Declarations

Conflict of interest The authors declare no conflicts of interest in the present work.

Human rights All procedures followed in this study were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Informed consent Informed consent was obtained from the patient for publication of this case report.

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