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Two-stage resection of a bilateral pheochromocytoma and pancreatic neuroendocrine tumor in a patient with von Hippel-Lindau disease: A case report

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ABSTRACT

INTRODUCTION: von Hippel-Lindau disease (vHL disease) is a hereditary disease in which tumors and cysts develop in many organs, in association with central nervous system hemangioblastomas, pheochromocytomas, and pancreatic tumors. We herein report a case of vHL disease (type 2A) associated with bilateral pheochromocytomas, pancreatic neuroendocrine tumors (PNET), and cerebellar hemangioblastomas treated via pancreatectomy after adrenalectomy.

CASE PRESENTATION: A 51-year-old woman presented with a cerebellar tumor, bilateral hypernephroma, and pancreatic tumor detected during a medical checkup. 18F-fluorodeoxyglucose positron emission tomography-computed tomography revealed a bilateral adrenal gland tumor and a tumor in the head of the pancreas, while an abdominal computed tomography examination revealed a 30-mm tumor with strong enhancement in the head of the pancreas. Cranial magnetic resonance imaging showed a hemangioblastoma in the cerebellum. Therefore, a diagnosis of vHL disease (type 2A) was made. Her family medical history included renal cell carcinoma in her father and bilateral adrenal pheochromocytoma and spinal hemangioblastoma in her brother. A detailed examination of endocrine function showed that the adrenal mass was capable of producing catecholamine. Treatment of the pheochromocytoma was prioritized, and therefore, laparoscopic left adrenalectomy and subtotal resection of the right adrenal gland were performed. Once the postoperative steroid levels were replenished, subtotal stomach-preserving pancreatoduodenectomy was performed for the PNET. After a good postoperative course, the patient was discharged in remission on the 11th day following surgery. Histopathological examination findings indicated NET G2 (MIB-1 index 10–15%) pT3N0M0 Stage II A and microcystic serous cystadenoma throughout the resected specimen. The patient is scheduled to undergo treatment for the cerebellar hemangioblastoma.

CONCLUSION: A two-staged resection is a safe and effective treatment option for bilateral pheochromocytoma and PNET associated with vHL disease.

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1. Background

Von Hippel-Lindau disease (vHL disease) is an autosomal dominantly inherited disease in which multiple neoplastic lesions

develop in many organs. Of these, 8–17% are associated with pancreatic neuroendocrine tumors (PNETs) [1]. We encountered a case of concomitant bilateral adrenal pheochromocytoma, PNET, and cerebellar hemangioblastoma, which necessitated a two-stage resection for the abdominal lesions. This work has been reported in line with SCARE criteria [2].

2. Case presentation

A 50-year-old woman visited our outpatient clinic owing to cranial lesions, bilateral adrenal lesions, and pancreatic lesions detected during a medical checkup. She had no previous medical

Abbreviations: vHL, Von Hippel Lindau disease; PNET, pancreatic neuroendocrine tumor; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography-computed tomography; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

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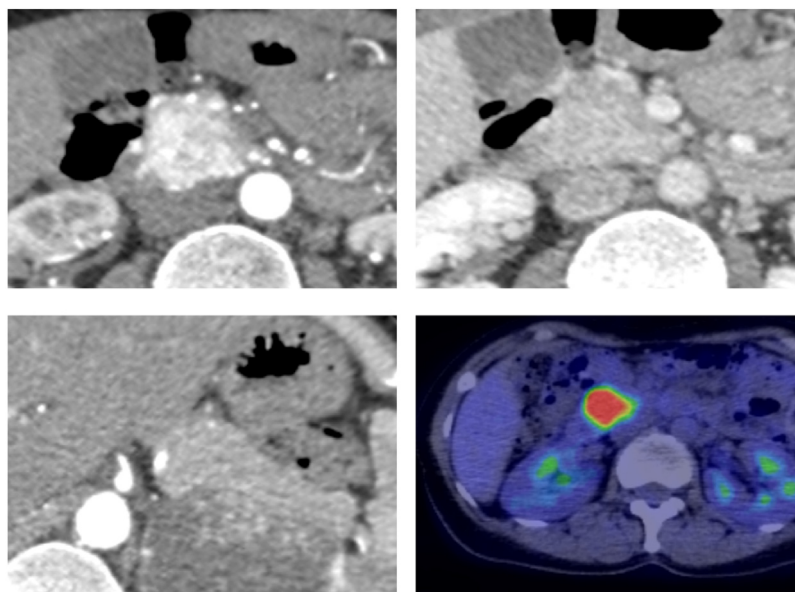


Fig. 1. Imaging findings.

The arterial phase enhanced, multi-detector computed tomography image shows well-enhanced tumors in the head of pancreas, along with high 18F-fluorodeoxyglucose accumulation, but no mass in the body and tail.

history. Her family medical history included renal cell carcinoma in her father and bilateral adrenal pheochromocytoma and spinal hemangioblastoma in her brother. Blood and urine tests were performed at the first visit; the 24-h urine sample showed abnormal normetanephrine levels (2.3 mg/day).

Abdominal contrast-enhanced CT showed a 2.5-cm pleomorphic tumor in the head of the pancreas (Fig. 1). Positron emission tomography–computed tomography demonstrated a 7-cm tumor in the upper pole of the left kidney, with 18F-fluorodeoxyglucose (FDG) accumulation localized to the margin, indicating a mural nodule. T1-weighted contrast-enhanced magnetic resonance imaging of the head demonstrated a high signal intensity area measuring 10 mm in the region from the cerebellar vermis to the left cerebellar hemisphere, indicating hemangioblastoma. Therefore, the patient was diagnosed with vHL disease type 2A simultaneously associated with bilateral pheochromocytomas, PNET, and hemangioblastomas. Owing to the presence of a functional pheochromocytoma, the patient's hemodynamics were unstable. After establishing stable blood pressure control using an $\alpha 1$ receptor antagonist in the Department of Endocrinology, laparoscopic left adrenalectomy and subtotal resection of the right adrenal gland was conducted as cortical sparing surgery in the Department of Urology. During the first surgery, single-incision open laparotomy of the umbilical region was performed. After detaching them from the surrounding organs, the bilateral adrenal gland lesions were excised. No increase in blood pressure was observed. After the first surgery, the clinical course was unremarkable, and the patient was discharged in remission on the sixth postoperative day. She was prescribed 10 mg of oral hydrocortisone to supplement the postoperative steroids; the dose was gradually reduced while screening adrenal function for ambulatory care. The administration of hydrocortisone was terminated 5 months after surgery. Subsequently, subtotal stomach-preserving pancreaticoduodenectomy with reconstruction was performed. Only minor postoperative adhesions were found around the Gerota's fascia with almost no adherence immediately under the wound. Moreover, the surgery was completed without high blood pressure or acute adrenal insufficiency. The patient's clinical course thereafter was unremarkable and she was discharged in remission on the 11th postoperative day. Currently, she is alive without recurrence at 2 years after surgery

for the bilateral adrenal pheochromocytoma and 6 months after the PNET surgery. Furthermore, no neurological symptoms such as paralysis or dizziness have been reported. However, the patient continues to undergo close observation in case the cerebellar lesion grows.

Pathologic findings showed a solid tumor with a white tone and a diameter of 25 mm in the head of the pancreas. Immunohistochemistry revealed positive results for chromogranin, synaptophysin, and CD56, with a Ki-67 index of 10–15%. Thus, the 2.5 × 1.5-cm pancreatic head tumor was classified as a T3N0M0 fStage II A NET G2 in accordance with the Union for International Cancer Control TNM 7th edition and WHO 2010 criteria (Fig. 2).

3. Discussion

vHL disease is an autosomal dominantly inherited disease complicated by multiple lesions. Of the tumors associated with vHL disease, renal cancer and central nervous system lesions are regarded as prognostic factors. PNET is associated with 8–17% of vHL diseases.

This report presents the first case of a secondary resection after laparoscopic cortical sparing surgery for intraperitoneal lesions due to type 2A vHL disease, which was simultaneously complicated by bilateral pheochromocytoma, PNET, and hemangioblastoma. However, the patient demonstrated good progress after surgery possibly owing to the following reasons: (1) upon resection of the bilateral adrenal pheochromocytoma and partial resection of the right adrenal gland, which preserved adrenal cortical function, pancreaticoduodenectomy could be carried out such that hormonal dynamics were almost normal; and (2) the postoperative clinical course was good and postoperative adhesion was reduced to a minor degree owing to the previous laparoscopic surgery.

A literature review yielded two similar reports in Japan that involved one-stage resections. Although it is difficult to simply compare findings, we concluded that patients undergoing a secondary resection would have no complications and that the hospitalization period is shorter. The merit of secondary resection is that the surgery can be carried out with stable hormonal dynamics. The demerits include (1) adverse effects caused by adhesion due to multiple surgeries and (2) delayed treatment for pancreatic lesions.

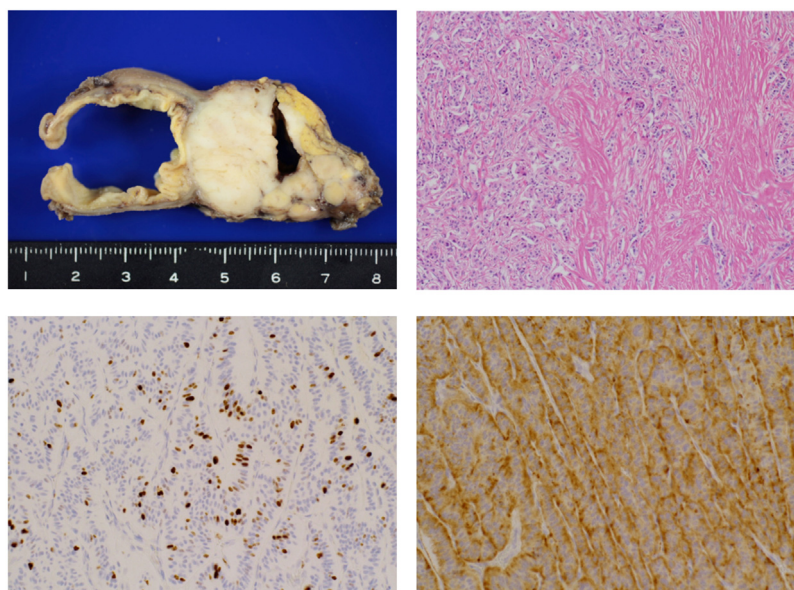


Fig. 2. Pathological findings.

The image shows a gross cross-section of the head of the pancreas demonstrating a solid and whitish mass. The solid tumor was a well-differentiated pancreatic endocrine neoplasm with clear cytoplasm (hematoxylin-eosin, $\times 200$). Many cells stained positive chromogranin, and the Ki-67 index was 10–15%.

Some previous reports recommend laparoscopic primary resection for multiple lesions [3]. According to these reports, secondary surgical strategies have the disadvantage of coincidence with the region of skin incision for abdominal lesions, making it difficult to conduct a second and subsequent surgeries due to adhesion. However, owing to laparoscopic surgery, postoperative adhesions can be expected to be relatively minor. Moreover, should the pancreatic lesion demonstrate malignant behavior, the period from diagnosis to resection is expected to be prolonged in cases of secondary resection, with the possibility of advancement of the disease. However, PNET associated with vHL disease does not have a high grade of malignancy [4]. Moreover, in cases of laparoscopic resection, recovery from primary surgery is expected to be quick. In our case, the interval between primary and secondary surgeries was 5 months, which is within an acceptable range.

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for PNET allows for a definite diagnosis of PNET and evaluation of malignancy, which can be used to guide secondary resection strategies. However, with PNET categorized as a heterogeneous tumor, the rate of concordance between the results of EUS-FNA and the final pathology is not high (74%) [5]. Additionally, owing to the complications of EUS-FNA treatment, the indication for EUS-FNA is believed to require careful consideration; thus, our department does not carry out EUS-FNA routinely. FDG-PET has been regarded as a preoperative evaluation tool for the grade of malignancy of PNET as a replacement for EUS-FNA. According to previous reports, the SUVmax from FDG-PET for non-hereditary PNET correlates with tumor pathology. On the other hand, PNET associated with vHL disease does not suggest a strong association with findings from FDG-PET [6], which are believed to be supplementary at this stage. It is necessary to develop treatment strategies taking into consideration the balance between short-term prognosis and long-term prognosis.

4. Conclusion

Two-stage resection is a safe and effective treatment for bilateral pheochromocytoma and PNET associated with vHL disease.

Conflicts of interest

No authors have conflicts of interest.

Sources of funding

There are no sources of funding for my research.

Ethical approval

The Institutional Review Board of Keio University Hospital approved this case report (reference number; 20120443).

Consent

The patient gave us the informed consent and accepted the publication of this case report.

Author contribution

Yutaka Endo, M.D. (data collection, drafting the article or revising it critically for important intellectual content).

Minoru Kitago, M.D., Ph.D. (drafting the article or revising it critically for important intellectual content, corresponding author and guarantor).

Akira Miyajima, M.D., Ph.D. (final approval of the version to be submitted).

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Taizo Hibi M.D., Ph.D., (final approval of the version to be submitted).

Chisato Takagi M.D., (data collection).

Yutaka Nakano M.D., (data collection).

Wataru Koizumi M.D., (data collection).

Osamu Itano, M.D., Ph.D., (final approval of the version to be submitted).

Yuko Kitagawa, M.D., Ph.D., FACS., (final approval of the version to be submitted).

Guarantor

Minoru Kitago is the guarantor for this study.

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