

## CASE REPORT

# Management of pancreatic gastrinoma associated with Von Hippel-Lindau disease: a case report

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### ABSTRACT

**Background:** Pancreatic neuroendocrine tumors (PNET) are a heterogeneous group and constitute 1.3% of all pancreatic tumors. Approximately 10% of these occur in the context of hereditary syndromes, such as VHL disease.

**Case report:** We report a case of a female patient of 37 years diagnosed VHL and intervened on several occasions by cerebral hemangioblastoma and renal carcinomas. During its follow-up she was diagnosed 2 gastrinomas functioning under 2 cm were enucleated. Later developed new PNET and underwent a total duodenopancreatectomy without pyloric preservation.

**Discussion:** The management of PNET in VHL is difficult due to the association of multiple tumors in different organs and the morbidity and mortality associated with the surgery of the pancreas. Management must be individualized for each patient, based on the ability to produce hormones and present symptoms, the size and location, and in the context of other tumors that usually present in these patients.

**Key words:** Von Hippel-Lindau. Neuroendocrine tumour. Pancreas. Gastrinoma.

### INTRODUCTION

Von Hippel-Lindau (VHL) disease is rare. It has an autosomal dominant pattern of inheritance, and is characterized by the development of tumors and cysts in various organs.

Tumors most frequently appear in the following organs: kidney (renal clear cell carcinoma) (25-60%), adrenal gland (pheochromocytoma) (10-20%), central nervous system (haemangioblastoma) (44-72%), eye (retinal angioma) (25-60%), inner ear (endolymphatic sac neoplasia) (10-25%), epididymis (cystadenoma) (25-60%), and pancreas (neuroendocrine tumors and cysts) (35-77%) (1,2).

Serous cysts are the most common lesion in the pancreas (70%) (3), while neuroendocrine tumors appear in 10-17% of cases (4), which are usually unique and non-functioning.

Unlike sporadic pancreatic neuroendocrine tumors, which are usually non-functioning, sporadic, and have a

high potential for malignancy (60-100%), pancreatic neuroendocrine tumors (PNET) related to VHL disease have a lower rate of metastasis. Because they do not secrete hormones, they produce no symptoms and are therefore usually diagnosed in advanced stages. Usually, patients with VHL disease undergo screening programs from a young age, allowing early diagnosis of PNET (5).

This case report presents a case of a functioning and malignant PNET in a patient with VHL disease and a multi-cystic pancreas.

### CASE REPORT

A 29-year-old female patient with VHL disease, with a ventriculoperitoneal shunt. She underwent two interventions for renal cell carcinoma (right kidney partial resection and radiofrequency of a nodule in the left kidney), and four resections of cerebral hemangioblastoma.

During follow-up, positron emission tomography-computed tomography (PET-CT) detected two pancreatic head lesions with a maximum standardized uptake value (SUV max) of 14.94 g/mL and multiple pancreatic cysts (Fig. 1). Next, a pancreatic functional study was performed, and revealed a high level of serum gastrin (2,319 pg/ml). Transgastric fine needle aspiration (FNA) yielded findings compatible with pancreatic neuroendocrine tumor.

With the diagnosis of two non-functioning gastrinomas sized less than 2 cm (T1N0M0, stage IV, differentiation grade G2, less than 2 mitoses per field, and Ki67 2-5%), a multidisciplinary committee decided that conservative surgery was indicated (6).

At surgery, after wide exposure of the pancreas, intraoperative ultrasound localized the two solid lesions at the pancreatic head and uncinate process, and enucleation with an ultrasonic dissector (CUSA) and harmonic scalping were performed. The postoperative course was uneventful.

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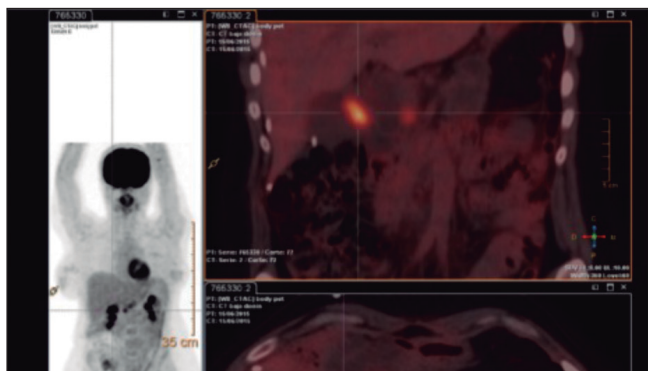


Fig. 1. PET-CT. Two hypermetabolic lesions, one in the head of the pancreas and one in the uncinus process adjacent to the superior mesenteric artery (before the first surgery).

Anatomopathological assessment revealed two moderately differentiated neuroendocrine tumors (G2) (chromogranin, synaptophysin and CD56+), with an index cell proliferation (Ki67) of 10% and atypical mitotic figures (1 mitosis in 10 high power fields). Postoperative gastrin level was significantly decreased, but still out of the normal range (1,383 pg/ml).

At 7 months follow-up, a new elevation of this biomarker was detected, as well as a high level of chromogranin A (181 ng/ml).

Although the Octreoscan did not reveal abnormal accumulation of activity, magnetic resonance (RM) and PET-CT showed growth of the left kidney tumor previously treated with radiofrequency and a new lesion in the pancreatic head in contact with the superior mesenteric vein (Fig. 2).

Given these findings, and in the context of a multi-cystic pancreas, the multidisciplinary committee decided to perform a total pancreaticoduodenectomy without pyloric preservation and associated splenectomy, with partial left kidney resection. To reconstruct bowel continuity, an end-

to-side transmesocolic gastrojejunostomy and an end-to-side hepaticojejunostomy Roux-en-Y were performed. It was necessary to perform a partial portal resection because it was not possible to identify a separation plane between the portal vein and pancreas. The portal vein was reconstructed with a continuous suture. The intraoperative biopsy ruled out vessel tumor infiltration (Fig. 3).

The histological report described a 9-mm pancreatic neuroendocrine tumor in the uncinus process, with moderate differentiation and without lymph node infiltration (0/8), and multiple cystic formations in the pancreas (multifocal and multicystic serous cystadenomas, with areas of serous-solid adenomas), and a 28-mm renal cell carcinoma.

During the postoperative course, the patient presented a caliceal urinary fistula requiring drainage by interventional radiology, which resolved after 2 months of follow-up (grade III complication according to the Clavien-Dindo classification).

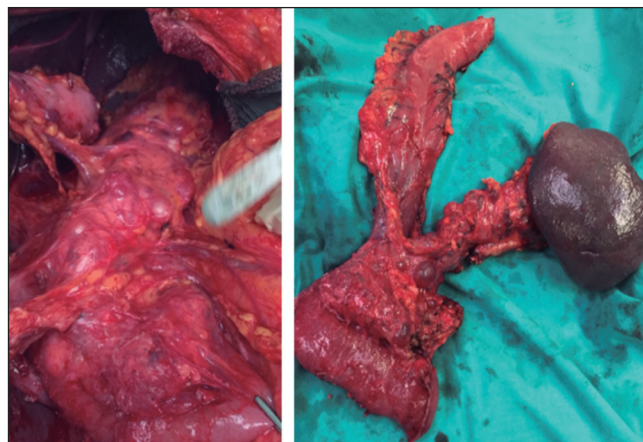


Fig. 3. Surgical specimen. Total duodenopancreatectomy associated with splenectomy.

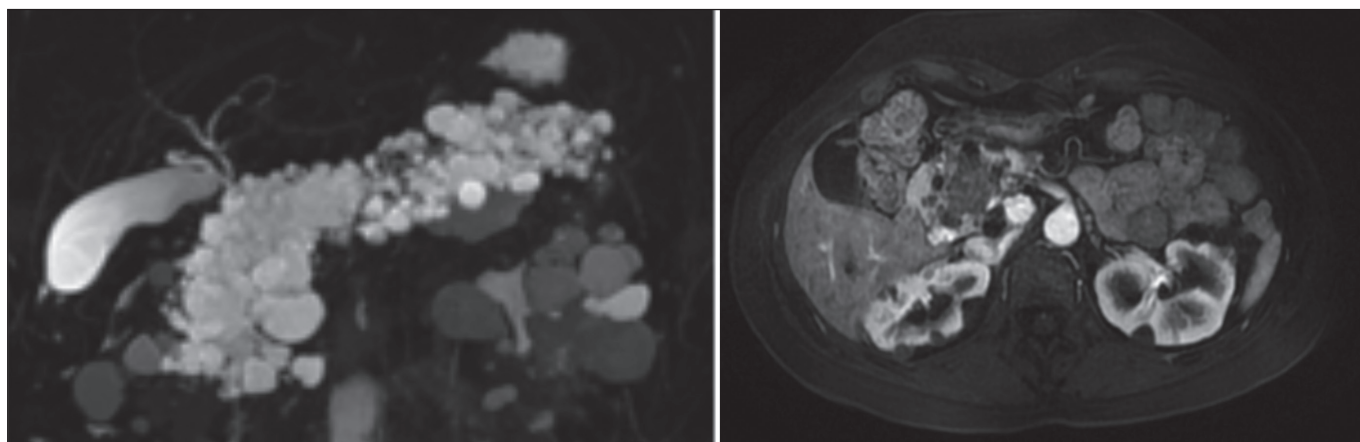


Fig. 2. MRI: multiple pancreatic cysts. Hyperintense lesion in contact with the superior mesenteric vein (before the second intervention).

## DISCUSSION

Pancreatic neuroendocrine tumors are a heterogeneous group, representing 1.3% of all pancreatic tumors.

Approximately 10% of these occur in the context of hereditary syndromes, such as VHL disease. PNET in patients with VHL disease has a better prognosis than sporadic PNET (10-20% and 60-90% of metastatic diseases, respectively).

These neoplasms may exhibit malignant behavior (5,7). They can be functioning or non-functioning. While the former clinically manifest in relation to secreted hormones, the latter usually have symptoms secondary to extrinsic compression of neighboring structures, or are detected as incidentalomas during examinations performed because of other diseases.

Hormonal, imaging, and histopathological tests must be performed to evaluate and diagnose PNET.

It is vital to assess the plasma levels of biochemical markers when diagnosing and monitoring patients with functioning neuroendocrine tumors.

In this case, a functional study revealed elevated gastrin levels, which dropped after the first surgery and increased again in subsequent controls, which helped in the detection of new recurrence.

Conventional imaging studies for PNET localization include endoscopic ultrasound, TC, and MRI. Radioactively labeled ligands are now available; these have led to major advances in the diagnosis, localization, and follow-up of these tumors. Octreotide scintigraphy and PET-TC (5) are complementary tests available for localization of these lesions. In this patient, the location was determined using PET-TC, whereas the Octreoscan results were found to be a false negative.

Managing PNET in patients with VHL disease is challenging because of the association of multiple tumors in different organs and the morbidity and mortality associated with surgery of the pancreas.

For asymptomatic tumors, some authors rely on size and location of the lesion for management, recommending follow-up with contrast-TC or RM every 12 months when lesions are smaller than 1 cm. In lesions sized 1-3 cm, management depends on location: surgical resection is indicated for tumors larger than 2 cm when located in the head of the pancreas, and in tumors larger than 3 cm when located in the body of the pancreas (4).

For functioning tumors, the recommended treatment is surgical resection regardless of size and location (2,9).

Blansfield et al. (4) proposed management depending on the likelihood of metastatic disease based on three factors: the presence of mutation in exon 3, size duplication time

of less than 500 days, and size larger than 3 cm. Patients who have none of these indicators are at little risk for metastatic disease and radiological follow-up is recommended every 2-3 years; if they have one of these indicators, monitoring is recommended every 6-12 months; and if they have two or three of these indicators, they are at high risk for metastatic disease and surgical resection is recommended (10).

Surgical treatment options range from enucleation, for small or low-grade tumors away from the pancreatic duct, to partial or total resection (9).

Surgery is the recommended management in case of tumor recurrence, as in this patient, when the tumor is able to be completely resected.

## CONCLUSION

Functioning neuroendocrine pancreatic tumors associated with VHL disease are rare. Management must be individualized for each patient, based on the ability to produce hormones and present symptoms, the size and location, and in the context of other tumors that usually present in these patients.

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