

## Role of Surgery in Metastatic ACTH-Producing Pancreatic Neuroendocrine Tumors

Emmanuel Gabriel, MD, PhD; Eisar Al-Sukhni, MD; Gissou Azabdaftari, MD; Moshim Kukar, MD, Steven Hochwald, MD\*

### \*Steven Hochwald, MD

Department of Surgical Oncology, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263 USA

Phone: 716 845 8244; Email: steven.hochwald@roswellpark.org

### Abstract

Metastatic adrenocorticotrophic hormone (ACTH) producing pancreatic neuroendocrine tumors (PNETs) comprise a rare but aggressive malignant disease, which is difficult to manage despite advances in modern treatment. Here we report a case of a metastatic ACTH-producing PNET treated with multimodal therapy, including surgical resection of the primary. The patient experienced symptom relief from surgical resection. Although this response was temporary, his recurrent symptoms were not to the extent as present prior to surgery. We present this case report with a discussion of the management of this disease, with emphasis on the role of surgery.

### Keywords

pancreas; neuroendocrine tumor; ACTH

### Introduction

While the incidence of ectopic adrenocorticotrophic hormone (ACTH) production outside of the pituitary gland is estimated to be 10% in patients with Cushing's syndrome, [1] the rate of ectopic ACTH from non-adrenal sites of origin is 3% and less than 1% for pancreatic neuroendocrine tumors (PNETs) in particular [2]. ACTH-producing PNETs are considered malignant and very aggressive, often presenting with synchronous metastases to the liver [3]. Thus, the prognosis of patients with these tumors is poor, particularly compared to patients with nonfunctional PNETs [2]. Even with multimodal therapy, including medical, liver-directed and surgical treatments, management of this disease is often challenging [4]. The rarity of this disease also limits the strength of evidence available for treatment recommendations, as reflected by the latest version of the guidelines recently set forth from the National Comprehensive Cancer Network (NCCN) [5]. In this report, we present a case of metastatic ACTH-producing PNET and briefly discuss the multimodal management of this disease, with emphasis on the role of surgery.

### Case Presentation

The patient was a 71-year-old man with no significant past medical history. He initially presented to an outside hospital with acute onset of bilateral lower extremity pitting edema. Upon admission, he was hypertensive (blood pressure 180/110 mmHg) and hypokalemic (2.4 mEq/L). A contrasted computerized tomography (CT) scan abdomen and pelvis was performed, showing a 5 cm mass involving

the tail of the pancreas with abutment of the left adrenal gland (Figure 1A).

After repletion of potassium and initiation of anti-hypertensive medications, including spironolactone and clonidine, he was referred to our institution. Further laboratory investigation showed a plasma ACTH of 238.1 pg/mL (institutional range 7.2-63.3 pg/mL) and cortisol of 41.4 µg/dL (range 4.2-22.4 µg/dL). Serum renin, aldosterone and metenephrines were normal. The serum chromogranin A level was 10 nmol/L (range 0-5 nmol/L), and the serotonin and Ca19-9 levels were normal. An esophagogastroduodenoscopy with endoscopic ultrasound (EGD/EUS) was performed showing a 3.8 x 3.2 cm hypoechoic mass in the tail of the pancreas. A fine needle aspiration was performed, showing cells of neuroendocrine origin. The sample was positive for cytokeratin AE1/3, CD56, chromogranin A and synaptophysin. He also underwent an Octreoscan identifying multiple bilobar liver metastases. A liver protocol CT scan was performed (Figure 1B).

The patient was started on monthly subcutaneous lanreotide (dose 120 mg) injections. An interval CT scan showed stable disease but detected the development of a left lower lobe segmental pulmonary embolism (PE). He underwent insertion of an inferior vena cava (IVC) filter and was started on Xarelto. He required admission to our institution 3 months after diagnosis for worsening edema, hypertension and persistent electrolyte abnormalities. Diltiazem and metoprolol were added to his medications, and these resulted in improved control of symptoms.

The patient was presented at our multidisciplinary conference to discuss further treatment recommendations. Given his persistent symptoms and declining performance status, the consensus decision was to proceed with surgical resection of the primary tumor and address the liver metastases later with liver-directed therapy should he continue to be symptomatic. Chemotherapeutic options were not considered because of his age and on-going symptoms. He underwent an uncomplicated laparoscopic distal pancreatectomy and splenectomy with partial left adrenalectomy. His post-operative course was uncomplicated, and he was discharged on post-operative day 4.

At his two-week post-operative clinic visit, his edema had completely resolved, and his cardiologist had stopped his antihypertensive medications. His ACTH and cortisol levels had normalized. Final pathology was consistent with a 5.4 cm neuroendocrine tumor, grade 2. A total of 1/10 lymph nodes were involved. Final pathologic staging was pT3 N1 M1. Figure 2 illustrates the histopathology. Cells were positive for the same markers as the sample obtained from the fine needle aspiration. The Ki67 was 5%. The patient was restarted on maintenance lanreotide and was offered liver-directed chemoembolization. However, due to his improved symptoms, he opted for continued surveillance. At his three month follow-up visit, surveillance imaging with a CT scan showed stable metastatic disease to the liver. However, he experienced recurrence of the lower extremity edema and hypertension, requiring re-initiation of medical management. Although his symptoms relapsed, the extent of his symptoms were less severe than that prior to surgery. His edema was non-pitting, and the patient required only two antihypertensive drugs to manage his hypertension. After discussion with the patient and his multidisciplinary team, the consensus recommendations included continued medical management. Surveillance imaging and serum ACTH and cortisol levels were recommended in 3 months, or earlier should his symptoms worsen.

## Discussion

In this case report, we described a rare case of a metastatic ACTH-producing PNET treated with multimodal therapy, including surgical resection of the primary in order to provide symptomatic relief of ectopic ACTH Cushing syndrome. The rate of ectopic ACTH-producing tumors originating from the pancreas has been reported to be less than 1%, [2] and thus the rarity of this disease reflects the challenges in its diagnosis and treatment. Whereas our patient was a 71-year-old male, this disease more often occurs in middle-aged women [4]. In our case, the patient presented with some features of Cushing syndrome, namely hypertension and lower extremity edema. There were also significant elevations in the serum ACTH and cortisol levels. Interestingly, there have been reported cases of elevated CRH in the serum as well [6,7], although this was not specifically measured for our patient. Localization of the primary tumor was achieved with a CT scan, and detection of metastases was found with an Octreoscan and further characterized with a liver protocol high-resolution, 3-phase CT scan. Other imaging modalities to localize the primary tumor and metastases have been described, including magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) [8,9]. However at our institution, we favor use of high-resolution contrasted CT imaging.

Pathologic diagnosis is assisted with immunohistochemical stains [5]. As this was a neuroendocrine tumor, it was positive for several markers expressed in tissues derived from neural origin on both the FNA and the final surgical specimen. These included cytokeratin, CD56, synaptophysin and chromogranin A [10,12]. Other special stains have been described, particularly for use in distinguishing PNETs from other rare pancreatic tumors such as pancreatic acinar cell carcinoma. These stains include ACTH itself,  $\beta$ -endorphin, trypsin and BCL10 [13]. Routine use of ACTH staining is not required for the diagnosis in the presence of clinical features consistent with a functional PNET. Therefore, ACTH staining was not performed because the patient had elevated levels of ACTH and cortisol, a biopsy proven PNET, symptoms consistent with Cushing syndrome, and relief of symptoms with normalization of the ACTH level following resection of the primary tumor.

After establishing the diagnosis, the more pressing challenge is the treatment of this tumor. As discussed, ACTH-producing PNETs are very aggressive with a propensity to metastasize synchronously to the liver and are associated with poor overall survival. Management includes both symptom control and minimizing the disease burden. Treatment of symptoms includes not only addressing the symptoms themselves but also the inherent goal of controlling plasma levels of cortisol. Symptom control is comprised of medical management, including antihypertensives and diuretics. Modulation of ectopic ACTH secretion may be obtained with somatostatin analogues such as octreotide and lanreotide, which target somatostatin receptors expressed on the surface of PNETs. Unfortunately similar to our case, many patients are refractory to these treatments, whereby the levels of circulating cortisol are often not affected [14,15]. The newer generation agent pasireotide, a multi-receptor targeted somatostatin analog, can be helpful in approximately 25% of patients who do not respond to the earlier agents [16]. Several different chemotherapeutic options have also been used for metastatic PNETs, including everolimus, sunitinib, capecitabine, temozolomide and rapamycin, with the goal of decreasing or stabilizing the growth of tumor lesions. The efficacy and toxicities of these various drugs have been discussed in a few previous case reports [4,17]. Since our patient was not considered appropriate for these treatments due

age and performance status, in this report we do not present a detailed discussion regarding systemic therapy for this disease.

Surgery to remove the primary tumor can result in symptom control, although this benefit is usually temporary [3,18]. The cure rate from surgery has been estimated to be between 30-47% of patients when synchronous metastases are not present [1]. As in our case where the patient had synchronous liver metastases, persistent disease contributed to the relapse of his symptoms. For patients without synchronous metastases, even after the resection of the primary tumor, metachronous development of metastatic disease has been reported resulting in symptom relapse [17]. In these instances, there are liver-directed options that may be effective, particularly ablation and transhepatic arterial embolization. Two case reports have reported improved symptom control for as long as 20 months following liver-directed therapy [19,20]. Overall response rates of 75% or higher have been reported for embolization, which can be further increased with the addition of medical therapy [20]. However, the durability of these responses are unclear. Furthermore as it pertains to ACTH-producing PNETs, these rates are based on relatively small retrospective case series or case reports. Thus, there are limitations in the applicability of liver-directed therapy to patients with metastatic ACTH-producing PNETs as a whole. Had our patient agreed to liver-directed therapy, in addition to ongoing medical treatment he would have been offered a combination of both embolization and ablation given the widespread liver disease involving both central and peripheral locations. We support the notion that the use of liver-directed therapy should be highly individualized and performed in a multidisciplinary setting.

## Conclusion

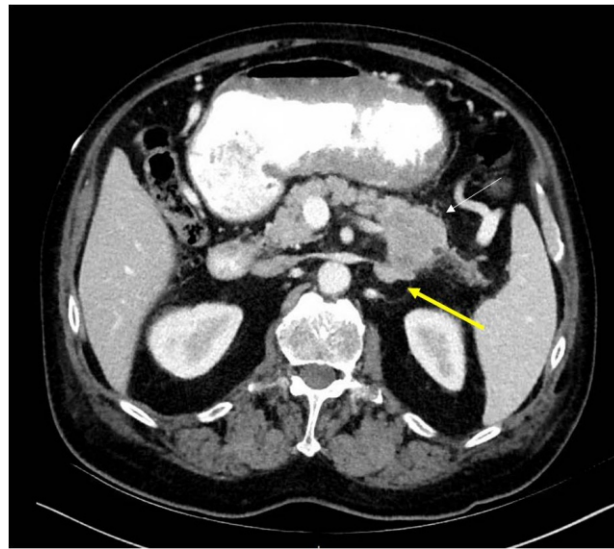
The management of metastatic ACTH-producing PNETs continues to be very challenging. Although there are many treatments in the armamentarium used for symptom and disease control for this rare entity, these PNETs tend to be very aggressive. In our case and others, surgery had a beneficial role in the symptom relief of this patient to the point that he no longer required antihypertensives. However, similar to the few reported cases, this relief was temporary. Although the extent of symptoms were not as severe as they were prior to surgical resection, the symptoms did relapse. He therefore continues with lanreotide and surveillance of his liver metastases with the option of undergoing liver-directed therapies. We argue that although the role of surgical resection of the primary tumor for metastatic ACTH-producing PNETs is limited in long-term symptom control, surgery offers an immediate means of symptom relief and can be a viable treatment for patients with limited systemic options. The decision to offer surgical resection of the primary ACTH-producing PNET should be made on a selective, individualized basis in the setting of a multidisciplinary team approach.

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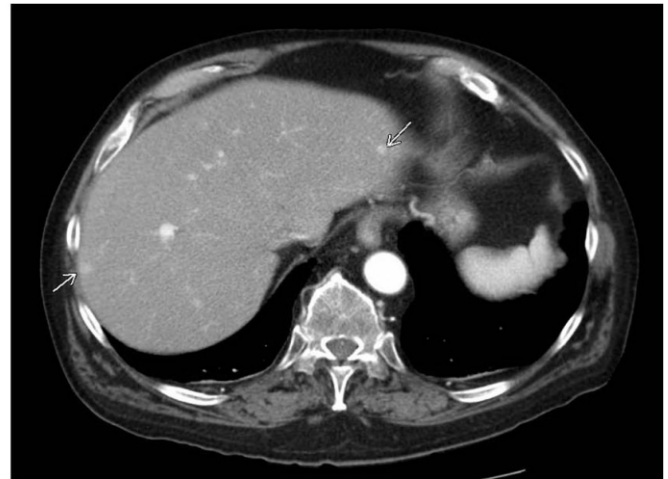
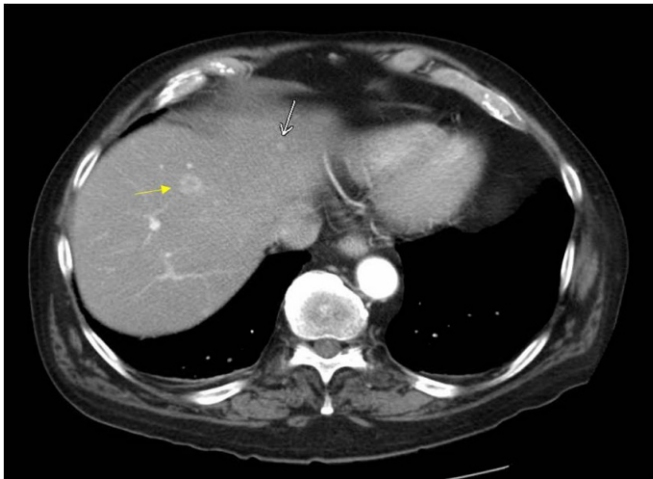
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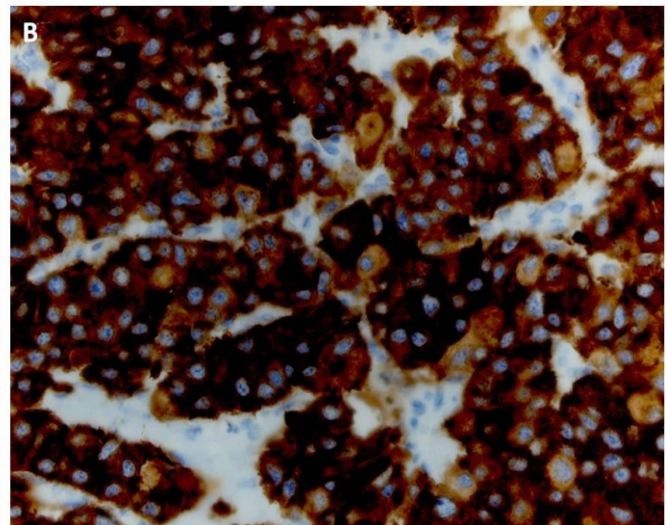
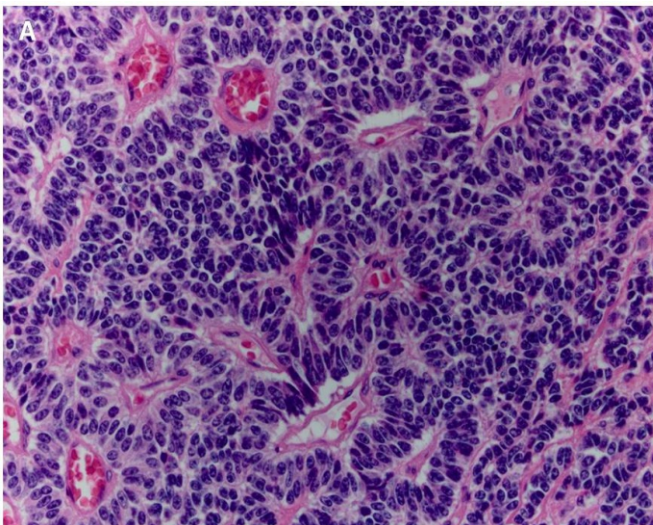
## Figures



**Figure 1 (A):** CT scan showing a 4 cm mass in the tail of the pancreas (white arrow) with abutment of the left adrenal gland (yellow arrow). The distal tail of the pancreas was atrophied, and the pancreatic duct at this portion was dilated.



**Figure 1 (B):** On liver protocol high-resolution CT imaging, multiple bilobar metastases were present throughout the liver as shown by enhancing discrete round lesions (white arrows) on the arterial phase. Some of the larger lesions showed a hyper-enhancing rim and area of central hypodensity (yellow arrow).



**Figure 2:** Histopathology illustrating the ACTH-producing PNET. (A) High power 400x magnification hematoxylin and eosin (H&E) staining of the specimen, which showed effacement of normal pancreatic tissue with atypical plasmacytoid cells with small, round or ovoid nuclei. (B) The specimen showed diffuse positivity for synaptophysin staining.

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**Authors Information:** Emmanuel Gabriel, MD, PhD<sup>1</sup>; Eisar Al-Sukhni, MD<sup>1</sup>; Gissou Azabdaftari, MD<sup>2</sup>; Moshim Kukar, MD<sup>1</sup>, Steven Hochwald, MD<sup>1\*</sup>

<sup>1</sup>Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263 USA

<sup>2</sup>Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY 14263 USA

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