Case Report

Case Report: Peri-operative management of ACTH-secreting pancreatic neuroendocrine tumor and major vessel reconstruction

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Abstract

Adrenocorticotrophic hormone (ACTH)-secreting pancreatic-neuroendocrine-tumors are extremely rare. They present a significant peri-operative management challenge because of the tumor's extensive vascular involvement as well as excess hormone production resulting in electrolyte and metabolic disturbances.

A 49-year-old male presented for resection of his ACTH-secreting pancreatic-neuroendocrine-tumor involving the pancreatic head and many major vessels. Pre-operative assessments showed increased serum cortisol, low serum ACTH, negative 24-hour urine 5-hydroxyindoleacetic-acid, and no suppression with 1mg dexamethasone. Pre-operatively, he had ectopic Cushing's syndrome, type II diabetes mellitus, hypokalemia and thrombocytopenia for which he was treated with insulin, intravenous potassium, and platelets. He was given octreotide at the beginning of surgery. The 10-hour procedure involved both general and vascular surgery. There was eight liters of blood loss and the patient required significant transfusions. At the end of surgery, he remained ventilated due to the duration of surgery and amount of blood loss. Post-operatively, he did well, but he developed adrenal insufficiency secondary to removal of his ACTH-secreting tumor and was discharged home on hydrocortisone.

This case highlights the role of anesthesiologists as the peri-operative physician in maintaining homeostasis in these complex patients. It also shows the importance of pre-operative tumor characterization, carcinoid crisis prophylaxis, and a multi-disciplinary approach to the management of these rare tumors.

Keywords: Pancreatic neuroendocrine tumors, Multidisciplinary perioperative management, Ectopic Cushing syndrome

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Case presentation

A 49-year-old male initially presented with a one-month history of generalized epigastric abdominal pain. He was investigated in the emergency department with an ultrasound which showed a vague abnormality in the pancreas region. Thus, a computed tomography scan of the abdomen was completed, showing a 9.5cm by 9.2cm pancreatic neck mass with multiple vascular involvements including the celiac artery, hepatic artery, left gastric artery, and splenic artery, as well as the superior mesenteric veins and splenic veins. Figure 1 displays a coronal view of the computed tomography scan completed. Based on the images and location, he was suspected to have a pancreatic neuroendocrine tumor. As such, he was referred to the hepatobiliary surgery service for pancreatoduodenectomy with vascular reconstruction.

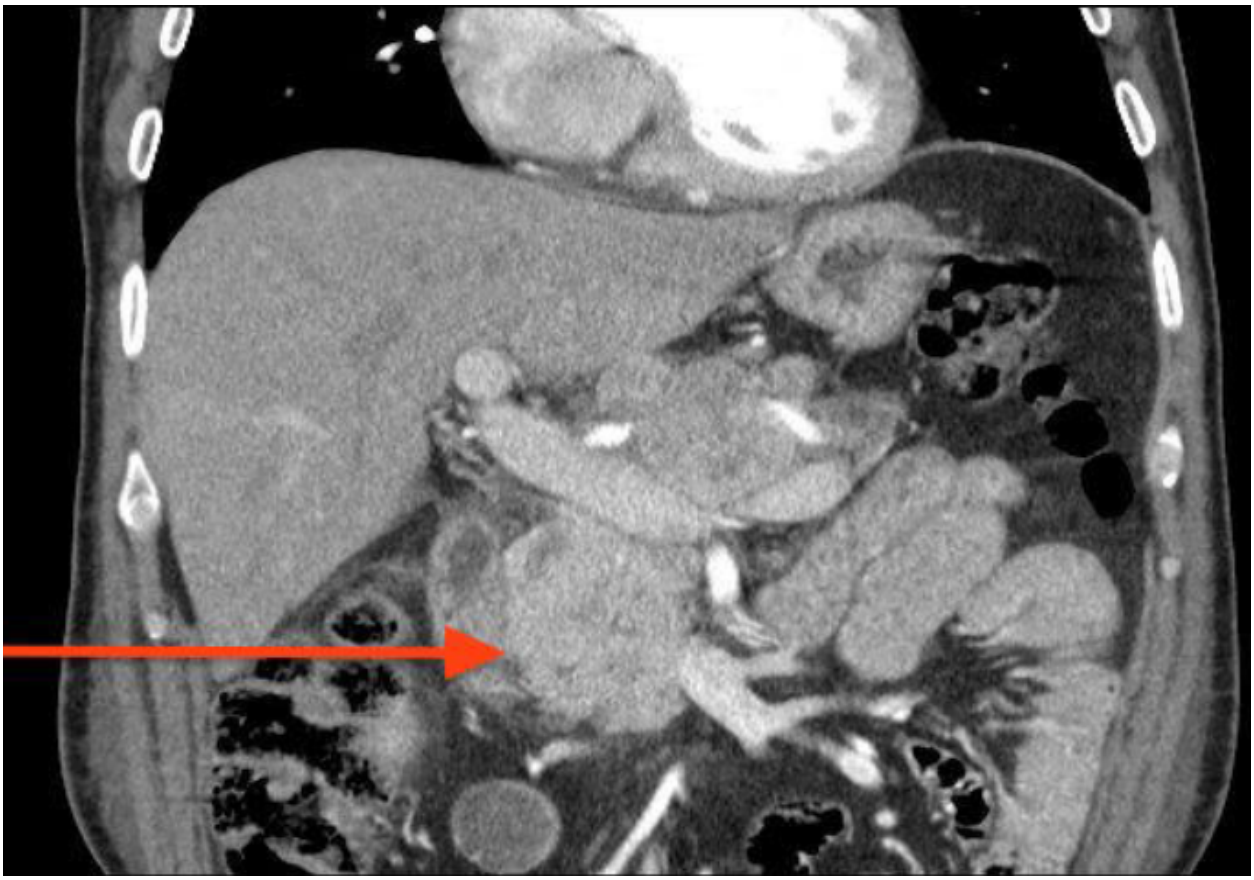

Figure 1. Coronal view of the computed tomography scan completed with a red arrow indicating the pancreatic head mass visualized.

Diagnosis

Further workup showed increased serum cortisol, low serum ACTH, and no suppression with one milligram of dexamethasone. The 24-hour urine collection was negative for 5-hydroxyindoleacetic-acid and the multiple endocrine neoplasia type I screen was negative. Upon

further questioning, he endorsed face and arm swelling, easy bruising, hyperpigmentation in the upper part of his thorax, and weight gain. He also complained of decreased sexual function with no sex drive and some erectile dysfunction over the last two months even though he has had no fertility issues in the past. Based on the testing results and his signs and symptoms, he was diagnosed with ectopic Cushing syndrome.

Management

A couple of weeks prior to his scheduled surgery date, he presented to the emergency department with generalized weakness and peripheral edema. Subsequent bloodwork revealed hypokalemia with a serum potassium less than two as well as hyperglycemia. He was admitted. Endocrinology was consulted and this patient was started on both potassium replacement and insulin therapy.

Hematology was also consulted for thrombocytopenia (platelet count of 52x 10^9/L). A thorough work-up was conducted and the thrombocytopenia was thought to be due to congestive splenomegaly secondary to splenic artery and vein involvement. One unit of platelets was transfused prior to surgery.

In addition to standard pre-operative testing, he had an echocardiography completed which was normal. On the day of surgery, the patient had standard monitoring. Induction was completed using midazolam, sufentanil, propofol, and rocuronium and the patient was placed on desflurane for maintenance of anesthesia. Following induction, a right radial arterial line and right internal jugular central line were placed. A 16-guage peripheral intravenous access was established and connected to a Level 1® fluid warming device. 100mcg of octreotide was given subcutaneously at the start of the case.

The surgery lasted 10 hours. It consisted of a pancreaticoduodenectomy with dissection and repair of many major vessels including the celiac artery, hepatic arteries (common, right, and left hepatic arteries), as well as the splenic artery and vein. The patient had an estimated eight liters of blood loss and received two units each of packed red blood cells, fresh frozen platelets, and cryoprecipitate.

Throughout the case, glucose levels were monitored hourly and subcutaneous insulin was given to keep levels between eight to 10 mmol/L. Electrolytes were also monitored. Hypokalemia was treated with intravenous potassium.

Outcome of the case

At the end of the case, the decision was made to keep the patient ventilated and transfer him to the intensive care unit because of the massive transfusion and long duration of surgery. Post-operatively, he developed adrenal insufficiency secondary to removal of his ACTH-secreting tumor. The endocrinology team was consulted to initiate hydrocortisone therapy. He was discharged home on post-operative day 32 on a tapering dose of hydrocortisone.

Review of the literature and discussion

Background information

Neuroendocrine tumors (NETs) arise from neuroendocrine cells that have properties of both nerve cells and hormone-producing cells. Thus, NETs are capable of releasing hormones into the blood. NETs can be classified as functional or non-functional depending on whether or not they produce these excess hormones (1).

Pancreatic neuroendocrine tumors (PNETs) are a rare subset of NETs originating from hormone producing islet cells (2). PNETs have an estimated incidence of less than one per 100,000 individuals and represent 1.3% of all pancreatic neoplasms (3). Functional PNETs are even rarer, encompassing only approximately 10-30% of all PNETs (3). PNETs often occur sporadically, although they are associated with certain genetic conditions such as multiple endocrine neoplasia type I (1). Functional PNETs could be further classified by the type of hormone they secrete. Common hormones secreted by PNETs include insulin and gastrin, while adrenocorticotrophic hormone (ACTH)-secreting PNETs are extremely rare (3).

Patients presenting for surgical resection of PNETs present a significant management challenge because of many reasons. The rich blood supply to the pancreas means that extensive vascular involvement is common with these tumors (4). This puts the patients at risk for significant blood loss and fluid shifts. Additionally, the production and release of excess hormones by PNETs result in peri-operative electrolyte imbalances and metabolic disturbances that need to be managed carefully. Because of the rarity of ACTH-secreting PNETs, consensus statements such as the “Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs)” group all the rare functional PNETs, including other PNETs such as glucagon- and somatostatin- secreting tumors, into one category. Thus, this case report adds to the growing body of literature on the management of these patients (5).

Discussion of the case

This case report highlights many key principles in the peri-operative management of a rare ACTH-secreting PNET. Firstly, pre-operatively characterization of the type and hormone production of neuroendocrine tumors is important – this allows for proper management and treatment of hormone and electrolyte abnormalities. In the case of our patient, he had an ACTH-secreting PNET. ACTH is a releasing hormone normally secreted by the pituitary gland. Its primary function is to stimulate the release of glucocorticoid steroid hormones from the adrenal cortex. Ectopic ACTH secretion resulting in excessive glucocorticoid production is a very rare cause of Cushing syndrome (6).

Patients with Cushing syndrome often present with glucose intolerance or type II diabetes mellitus, owing to glucocorticoids’ antagonistic effects to insulin (6). Excess glucocorticoids have mineralocorticoid activity in the kidneys. This promotes sodium reabsorption and potassium excretion and results in hypokalemia (6). Characterizing the hormone production of

this patient's tumour allowed for proper peri-operative management of our patient's glucose levels and potassium levels.

Another important management principle is the consideration of carcinoid syndrome. Carcinoid syndrome is a paraneoplastic syndrome that occurs in approximately 19% of patients with neuroendocrine tumors (7). While it is more frequently associated with carcinoid tumors of the gastrointestinal tract and pulmonary tract, it can also result from PNETs. Carcinoid syndromes are characterized by diarrhea, flushing, wheezing, and/or skin lesions; however, more severe manifestations include carcinoid heart disease which occurs in 40% of patients (7). Thus, there should be a low threshold for performing a pre-operative echocardiography in this patient population.

Patients are also at risk for a carcinoid crisis. Carcinoid crisis could present with sudden changes in blood pressure – such as a hypertensive crisis from sudden release of catecholamines – excessive flushing, hyperthermia, and bronchospasm (7). Known triggers of carcinoid crises include the induction of anesthesia, minor and major procedures, and tumor manipulation during surgery. Thus, there is an increased risk of precipitating a crisis during the peri-operative period (7). Our patient was given a long-acting somatostatin analogue known as octreotide. Octreotide binds to somatostatin receptors on the PNET to control hormonal output and has been used as prophylaxis against carcinoid crisis (3). It has also been used peri-operatively to prevent the development of pancreatic fistula associated with pancreatic surgery (8).

This case report also highlights the importance of a multi-disciplinary team approach to the perioperative management of these cases. Radiological studies are important for evaluation of tumor extent and relation to adjacent anatomical structures; regional and distant metastases; and vascular involvement (9). Consultation of the endocrinology and hematology teams were needed for pre-operative optimization. A vascular surgery team was involved due to the major vascular extensions.

In summary, this case highlights the importance of pre-operative tumor characterization, carcinoid crisis prophylaxis, and a multi-disciplinary approach. It also demonstrates the significant role of the anesthesiologist in maintaining homeostasis in patients with complex metabolic derangements and significant blood loss.

Consent

This case report is published with written consent from the patient.

Acknowledgements

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References

1. Genetic and Rare Diseases Information Center: U.S. Department of Health & Human Sciences. Neuroendocrine tumor [Internet]. Gaithersburg, Maryland: Genetic and Rare Diseases Information Center; 2019. Available from: https://rarediseases.info.nih.gov/diseases/13445/neuroendocrine-tumor.

2. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469-1492.

3. Kaltsas G, Caplin M, Davies P, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre and Perioperative Therapy in Patients with Neuroendocrine Tumors. Neuroendocrinology. 2017;105: 245-254

4. Vinik A, Casellini C, Perry RR, et al. Pathophysiology and Treatment of Pancreatic Neuroendocrine Tumors (PNETs): New Developments. South Dartmouth: MDText.com; Inc, 2000.

5. Falconi M, Eriksson B, Kaltsas G, et al. EConsensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs). Neuroendocrinology. 2016;103(2):153–171.

6. Davies M, Hardman J. Anaesthesia and adrenocortical disease. Brit J Anaesth. 2005;5:122-126.

7. Ito T, Lee L, Jensen R. Carcinoid-syndrome: recent advances, current status and controversies. Curr Opin Endocrinol. 2018;25:22-35.

8. Alghamdi A, Jawas A, Hart R. Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: a systematic review and meta-analysis. Can J Surg. 2007;50:459-466.

9. Sundin A, Vullierme MP, Kaltsas G, Plöckinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. Neuroendocrinology. 2009;90:167-183.

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