Metastatic pancreatic neuroendocrine tumor with ectopic adrenocorticotrophic hormone production

Muthiah Vaduganathan, MD, MPH, Amulya Nagarur, MD, Darcy A. Kerr, MD, Kelly B. Lauter, MD, PhD, Arun Padmanabhan, MD, PhD, Srivatsan Raghavan, MD, PhD, Juan C. Pallais, MD, MPH, and Andrew Z. Fenves, MD

We describe a 71-year-old man who presented with abdominal pain, lower-extremity edema, recent unintentional weight loss, hypertension, hyperglycemia, hypokalemia, and metabolic alkalosis. Serum cortisol levels remained elevated after overnight high-dose dexamethasone suppression. Magnetic resonance imaging revealed a small mass in the head of the pancreas with scattered liver metastases. Both endoscopic ultrasound-guided pancreatic biopsy and liver biopsy revealed a well-differentiated neuroendocrine tumor. These lesions did not show significant uptake on octreotide scan. Medical management and hepatic artery chemoembolization were attempted. Ultimately, the patient underwent bilateral adrenalectomy, but died within 4 months of symptom onset secondary to postoperative complications.

Ectopic adrenocorticotrophic hormone (ACTH) production outside the pituitary gland occurs in approximately 10% of patients presenting with Cushing's syndrome (1). Pancreatic neuroendocrine tumors (NET) are a rare cause of ectopic ACTH syndrome. Herein, we present a case of metastatic pancreatic NET with ectopic ACTH production refractory to medical and surgical management.

CASE DESCRIPTION

A 71-year-old white man originally from Ireland with known hypertension, hyperlipidemia, and hypothyroidism was in his usual state of health until 2 months before admission when he experienced progressive functional decline. His ambulation was limited to less than half a mile on level ground and less than one flight of stairs. Over this time, he reported abdominal distension, moderate nonspecific abdominal discomfort, anorexia, and a 25-pound unintentional weight loss. Evaluation by his primary care physician included a normal colonoscopy. During these office visits, his blood pressure and blood sugar were elevated. Over the 2 weeks before admission, he developed progressive lower-extremity edema and was started on hydrochlorothiazide and spironolactone. Despite this, his abdominal distension and lower-extremity edema progressed, prompting admission to our hospital. Prior to this admission, he was taking aspirin, calcium, vitamin D, fluticasone nasal spray, lisinopril, and simvastatin. He was started on potassium citrate within the month prior to admission for persistent hypokalemia.

He reported an 80-pack year tobacco history and former heavy alcohol use (up to 12 beers daily). His mother and sister both died of gastric carcinoma at 57 and 38 years of age, respectively.

On presentation, he was afebrile, with a heart rate of 111 beats/minute, blood pressure of 155/86 mm Hg, and oxygen saturation of 94% on room air. He was in no apparent distress. He had a round, ruddy face with slight exophthalmos and right-sided facial droop (both of which preceded his current illness). Precordial exam revealed a soft systolic ejection murmur at the left upper sternal border. His lungs were clear to auscultation. His abdomen was protuberant and nontender to palpation. He had symmetric 2+/4+ lower-extremity edema that extended to the knees. No striae, moon facies, or proximal muscle weakness were appreciated.

Initial laboratory results disclosed potassium 1.8 mEq/L, bicarbonate 38.4 mEq/L, aspartate transaminase 124 U/L, alanine transaminase 189 U/L, alkaline phosphatase 157 U/L, and lipase 94 U/L. A contrast computed tomography (CT) scan of the abdomen disclosed multiple hypodense liver lesions (*Figure 1*), small 2- to 3-mm scattered pulmonary nodules, and a lumbar compression fracture.

His serum cortisol at 5:00 AM was 38.9 µg/dL with an ACTH level of 84 pg/mL. After overnight high-dose dexamethasone suppression, his 8:00 AM cortisol level remained elevated at 38.8 µg/dL. His initial 24-hour urine free cortisol was 371.5 mcg. Renin and aldosterone were below the detectable limits of testing. Analysis of tumor markers revealed a carbohydrate antigen (CA) 19-9 284 U/mL, beta-human chorionic gonadotropin 7.2 mIU/mL, carcinoembryonic antigen 8.7 ng/mL, and prostate-specific antigen 6.77 ng/mL.

Magnetic resonance imaging (MRI) of the brain revealed no pituitary abnormalities. An MRI of the abdomen showed a pancreatic head mass and multiple hepatic lesions. Endoscopic ultrasound-guided biopsy of the pancreatic mass showed predominantly nonneoplastic pancreatic and gastrointestinal tissue

From the Department of Medicine (Vaduganathan, Nagarur, Lauter, Padmanabhan, Raghavan, Pallais, Fenves) and the Department of Pathology (Kerr), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Corresponding author: Muthiah Vaduganathan, MD, MPH, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, GRB 740, Boston, MA 02114 (e-mail: muthu@md.northwestern.edu).

Figure 1. CT of the abdomen showing innumerable small hypodense hepatic lesions suggestive of metastatic disease.

with rare groups of atypical epithelioid to plasmacytoid cells, suspicious for well-differentiated NET (*Figure 2a*). Liver biopsy revealed a uniform population of plasmacytoid neoplastic cells with characteristic “salt and pepper” chromatin (*Figure 2b*). Cell block preparation of the liver mass showed neoplastic cells demonstrating positive immunohistochemical staining for synaptophysin (*Figure 2c*) and chromogranin. The ki-67 proliferative index was 35%. Stains for Pax-8, TTF-1, CDX-2, ACTH, and gastrin were negative. Octreotide scan did not show significant uptake within these lesions.

He was started on ketoconazole with improvement in serum cortisol, but this drug was discontinued due to worsening liver function. He was switched to metyrapone with urine free cortisol downtrending to a nadir of 67.9 mcg/day (range 17–47 mcg/day); however, this drug was also stopped for cost and insurance concerns. Despite continued high cortisol levels, the patient became symptomatic from steroid withdrawal, manifesting as fatigue and malaise, for which he received 1 mg of dexamethasone. The patient was maintained on octreotide acetate despite lack of uptake on octreotide scan. He underwent hepatic artery embolization on hospital day 18 without a significant effect on cortisol secretion. Due to persistently elevated cortisol levels, he underwent bilateral adrenalectomy

Figure 2. (a) Pancreatic biopsy reveals occasional groups of atypical epithelioid to plasmacytoid cells, suspicious for well-differentiated neuroendocrine tumor (Papanicolaou stain). (b) Liver biopsy shows a monomorphic population of similar-appearing neoplastic cells with round to oval nuclei and dispersed, finely stippled chromatin that are arranged as dispersed single cells with scattered pseudorosette formations (Papanicolaou stain). (c) Cell block preparation from the liver biopsy demonstrates strong immunoreactivity for synaptophysin in tumor cells (hematoxylin-eosin; inset: synaptophysin immunohistochemical stain). (d) Bilateral adrenal-ectomy specimens show multifocal metastatic neuroendocrine tumor in a background of diffuse adrenal cortical hyperplasia (hematoxylin-eosin).

Figure 3. Treatment-related changes in (a) UFC (normal range 0–55 mcg/24 hours), (b) serum cortisol (normal range 6–23 mcg/dL), and (c) serum ACTH (normal range 9–52 pg/mL) prior to bilateral adrenalectomy on hospital day 28. ACTH indicates adrenocorticotropic hormone; UFC, urine free cortisol.

on day 28 of hospitalization (*Figure 2d*). *Figures 3a to 3c* depict the erratic, uncontrolled levels of urine free cortisol, serum cortisol, and serum ACTH during his treatment course. His labile blood pressure and volume overload were controlled with escalating doses of spironolactone, captopril, labetalol, and furosemide.

Postoperatively, the patient was started on stress-dose steroids with intravenous hydrocortisone 100 mg every 8 hours. Following surgery, he experienced a number of postoperative complications including delirium, acute pancreatitis, enterococcal urinary tract infection, peripherally inserted central catheter-associated deep venous thrombosis, gastrointestinal hemorrhage,

and atrial fibrillation. Due to his rapid functional decline, the patient and his family chose to transition to a comfort-oriented care approach and he passed away on hospital day 42.

DISCUSSION

Ectopic ACTH production secondary to a pancreatic NET may have variable presentations, ranging from vague, nonspecific symptoms to more dramatic cases of diabetic ketoacidosis or hypertensive crisis (2). Many patients lack the traditional phenotypic features of Cushing's syndrome, but have prominent biochemical abnormalities, specifically hypokalemia, metabolic alkalosis, and hyperglycemia (3). The majority of patients are middle-aged women with limited comorbid diseases.

Pancreatic NET often presents with advanced, metastatic disease, similar to our case. Approximately 75% of cases of midgut or hindgut NET have known liver metastases (4). These cases are difficult to manage given early and aggressive tumor recurrence despite resection of the primary lesion. A minority of cases may respond to targeted medical therapies based on biochemical profiling of the tumor pathology (5–7). These indolent tumors are slower growing, and their localization often precedes ACTH secretion and the Cushingoid phenotype. Variations in clinical course can be ascribed to aggressive transformation of the tumor upon disease recurrence or liver metastases. NET may be biochemically heterogeneous and secrete multiple different hormones to produce distinct clinical phenotypes (8). We note that the pathology specimen in our patient did not stain positive for ACTH, which may be due to sampling error. Alternatively, cases of pancreatic NET secreting corticotropin-releasing hormone (CRH) have been described (9). The clinical picture is still one of Cushing's syndrome, though specific CRH staining must be sought.

Finding the source of ectopic ACTH production can be challenging, as these tumors are typically small and radiographically covert on routine CT imaging (10). Primary sites include the lung (bronchial carcinoids or small cell carcinomas), but can more rarely include the pancreas, thymus, gastrointestinal tract, and prostate (1, 10). In our case, MRI detected a pancreatic head mass, not seen on initial CT imaging. Somatostatin receptor imaging with tagged octreotide (11) and combined positron emission tomography/CT (12, 13) can further localize ectopic ACTH-producing tumors.

Managing ectopic ACTH production includes pharmacologic control of hypercortisolemia, bilateral adrenalectomy, and/or interventional or surgical resection of the secreting tumor or associated metastases. Resection of the primary tumor can be performed, but reported surgical success has been only modest (30%–50%) (1). Limited experiences support the safety and efficacy of early bilateral adrenalectomy in refractory cases (14). Thus, medical therapies represent the mainstay of initial management. Steroidogenesis can be directly inhibited by agents such as ketoconazole, metyrapone, mitotane, aminoglutethimide, ortho-paradichlorodiphenyldichloroethane, and etomidate (15). Ketoconazole has been effective in small case series; however, the majority of patients died of ketoconazole-refractory cortisol production within a median of 19 weeks

(16). Recently, it has been reported that inhibitors of ACTH production at the pituitary level with dopamine agonists have afforded effective control of cortisol levels (17).

Pancreatic NET may have specific treatment approaches. Somatostatin analogues (octreotide and lanreotide) target somatostatin receptors commonly expressed in pancreatic NET and can lead to decreased hormone production, although they often have limited tumor regression effects (18). Advanced pancreatic NET may be amenable to chemotherapeutic intervention, and early clinical data favor the use of everolimus (rapamycin inhibitor) (19) and sunitinib (tyrosine kinase inhibitor) for improvement in progression-free survival, although response rates are in the single-digit range (20). Streptozocin in conjunction with doxorubicin or 5-fluorouracil is approved for pancreatic NET, but is limited by its toxicity profile (21, 22). There are several small series testing capecitabine and temozolomide with response rates in the 40% to 70% range. Palliation of unresectable tumors may be achieved with hepatic arterial embolization with improvement in symptoms and reduction in overall tumor burden (4). Unfortunately in our patient, hypercortisolemia persisted despite available medical and surgical interventions.

Pancreatic NET can have variable, often aggressive endocrinologic manifestations. A high index of suspicion is required for early diagnosis given the vague, undifferentiated initial presentation. Tumor heterogeneity and a rapidly progressive course can pose significant management challenges. A multidisciplinary team can tailor treatment strategies to target biochemical tumor features.

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