Pancreatic Neuroendocrine Tumor with Ectopic Adrenocorticotropin Production: A Case Report and Review of Literature

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Abstract. *Pancreatic neuroendocrine tumors (p-NETs) entail a vast array of tumors, which can vary from benign neoplastic growths to rapidly aggressive malignancies. Such is the case with ectopic adrenocorticotropic hormone (ACTH)-producing p-NETs. These tumors have been found to be quite aggressive and a challenge to treat, especially due to the occurrence of metastatic disease even after resection of the primary tumor. We discuss the case of a 44-year-old female who initially presented with vague, non-specific symptoms, in which a malignant p-NET was found to be the cause of her clinical presentation. Although resection of the pancreatic mass was performed, the patient presented again with metastatic disease to the liver.*

Pancreatic neuroendocrine tumors (p-NETs) are incredibly rare and those that are responsible for ectopic adrenocorticotropic hormone secretion are even more uncommon, and carry a poor prognosis (1). As a whole, gastroenteropancreatic system neuroendocrine tumors have an annual incidence of only 1-2/100,000 and they are most commonly caused by insulinomas and gastrinomas. Other NETs, such as glucagonomas, somatostatinomas, vasoactive intestinal peptide (VIP)omas, and pNETs causing ectopic adrenocroticotropic hormone (ACTH) syndrome (EAS) have a rare occurrence (2). EAS is noted to be responsible for 10-20% of Cushing's syndromes and can be caused by multiple

tumors, most commonly small cell carcinomas (3). Other indolent EAS-associated tumors include pancreatic, bronchial and thymic carcinoid tumors, medullary thyroid carcinoma and pheochromocytoma (1). EAS makes up a mere 7% of all pancreatic endocrine tumors and is generally extremely aggressive (4).

Staging and grading of NETs has proven to be quite cumbersome, primarily because within the entity of gastroenteropancreatic NETs, there is a vast array of differences in the appearance and behavior of each encountered tumor. NETs are heterogeneous in their morphology and thus in their behavior, and subsequently their prognosis, which is most clinically pertinent to the care of patients. As a result, societies such as the World Health Organization and the European Neuroendocrine Tumor Society have proposed distinct ways to classify each tumor to help differentiate malignant entities from benign ones. The World Health Organization classifies NETs based on the degree of metastatic disease, Ki-67 index, and mitotic count index, histology, vascular invasion, and tumor size (5). The European Neuroendocrine Tumor Society also uses Ki-67 index and mitotic count index, and TNM classification, allowing for each tumor to be differentiated into one of three groups: G1, G2 and G3 (6, 7).

Case Report

In November 2007, a 44-year-old female with diabetes mellitus type 2, hypertension, and hyperlipidemia, presented to an outside hospital with complaints of several months duration of progressive fatigue and bilateral lower extremity weakness. Examination revealed a chronically ill-appearing female with hyperpigmented papules over her face and abdomen, abdominal striae, and thin upper and lower extremities. Initial laboratory studies revealed hyperglycemia,

hypokalemia, and hypercalcemia. Cortisol and ACTH levels were elevated. The diagnosis of Cushing's syndrome was established by dexamethasone suppression testing. Computed tomographic (CT) scan detected a large mass at the tail of the pancreas. Subsequent staging scans were otherwise negative for suggestion of distant metastatic disease. CT-guided biopsy of the mass and subsequent pathological analysis revealed a clear cell neuroendocrine tumor positive for cytokeratins, synaptophysin, neuron-specific enolase (NSE), neural cell adhesion molecule (CD56), chromogranin, inhibin, and vimentin. Immunohistochemical staining for glucagon was equivocal. The tumor was negative for gastrin, somatostatin, ACTH, renal cell carcinoma antigen, and CD10 (common acute lymphoblastic leukemia antigen).

After correcting her electrolyte abnormalities and stabilizing the patient, surgical resection of the pancreatic mass was considered. The patient underwent pre-treatment with ketoconazole and metayrapone. Open distal pancreatectomy and splenectomy were performed in December 2007. Reportedly, the entire tumor was removed, with margins being negative. There were no obvious signs of metastatic disease upon direct visualization. Her post-operative course was complicated by the development of a left lower extremity deep-vein thrombus. She was started on anti-coagulation but manifested bleeding from her operative site. This necessitated the placement of an inferior *vena cava* filter, with anti-coagulation being discontinued. She was subsequently discharged to a rehabilitation facility. She did well from a physical standpoint; however, she had very limited follow-up with her primary surgical and endocrine providers, was and then lost to follow-up for about one year.

In February 2009, she presented to her primary surgical provider approximately two years from her original diagnosis. A CT scan was performed and showed new arterially-enhancing lesions within the liver. Comparison imaging studies from two years prior did not show these enhancing lesions. Her endocrine care was transferred to Tufts Medical Center at which time her Chromogranin A and ACTH levels, and a 24-hour urinary-free cortisol were normal. Serum cortisol suppressed to 1.1 μg/dl with a low dose dexamethasone suppression test. However, pancreatic polypeptide was slightly elevated at 556 pg/ml (normal range=70 to 430 pg/ml). An octreotide scan was negative for uptake of radiolabeled octreotide.

In June 2009, the patient was seen by Gastroenterology Oncology. She continued to remain asymptomatic, and a CT scan showed stability of her hepatic lesions. However, in December 2009, a CT scan showed progression of multiple lesions within the liver. A subsequent octreotide scan was negative for uptake, with a serum pancreatic polypeptide level remaining elevated at 479 pg/ml. She underwent an ultrasound-guided core needle biopsy of the liver. Pathological analysis did not yield a malignancy.

The patient was again lost to follow-up and was not seen at the Division of Endocrinology until December 2012. Although she did not show Cushing syndrome her pancreatic polypeptide was elevated at 1221 pg/ml and she did not suppress ACTH or cortisol with low dose dexamethasone (ACTH 61pg/ml, cortisol 10.2 μg/dl, dexamethasone level 330 ng/dl). There was worsening of her diabetes mellitus and she was found to be severely iron-deficient. After a thorough work-up of her iron deficiency, she was started on intravenous iron replacement therapy. A magnetic resonance imaging (MRI) study of the liver was performed and confirmed multiple arterially-enhancing lesions within the right and left lobes. Another octreotide scan was obtained and notable for marked uptake of radiolabeled tracer within both lobes of the liver without evidence of extrahepatic involvement. Despite her liver involvement, the patient continued to remain asymptomatic with a preserved functional status. She was able to complete iron replacement therapy; however, her blood glucose remained difficult to control.

Options for management were discussed with the patient. Starting the patient on oral capecitabine and temozolomide was considered per the experiences of Fine *et al.* (8). However, after discussing the case with the endocrinology, surgery, and interventional radiology team, the decision was made to proceed with subcutaneous octreotide therapy as a bridge to a potential radioembolization with yttrium-90 (Y90) microspheres of any residual hepatic disease. Evidence of benefit with octreotide was extrapolated from the PROMID study trial, a placebo-controlled, randomized trial that showed the use of octreotide LAR can be successful in controlling midgut NET growth and further corroborated through the experiences of Kondo *et al.* (1).

In early April 2013, the patient was started on octreotide at 50 μg *s.c.* three times per day and subsequently transitioned to octreotide LAR 20 mg intramuscularly once per month. Within two months of treatment, her pancreatic polypeptide, ACTH and urinary-free cortisol levels normalized and she underwent Y90 radioembolization. The patient tolerated the procedure well and there were no immediate complications.

Discussion

Among other NETs, EAS caused by p-NETs are particularly aggressive. Metastatic disease, primarily to the liver, is commonly already established by the time Cushingoid features have developed (9). This may be due to the fact that the metastatic lesions are predominantly responsible for ACTH secretion, rather than the primary pancreatic lesion, resulting in diagnosis from a clinical presentation to occur late in the disease process. ACTH-producing p-NETs have also been noted to metastasize to the mediastinal and paraaortic lymph nodes, pelvis, hilus, hepatic portal region, and lungs (10).

Metastasis has been reported to occur even after resection of the primary pancreatic tumor, as was seen in the presenting case, making long-term surveillance essential to the patient's final prognosis. Due to the aggressive nature of this tumor, the two-year survival rate is approximately 60% and five-year survival rate is only 16% (11).

By the time a patient presents with EAS p-NET, they may demonstrate a number of Cushingoid features such as facial plethora, centripetal obesity, fatigue, striae, ecchymoses, proximal muscle weakness, memory impairment, skin pigmentation, hypertension, a variety of psychiatric symptoms including depression and psychosis, and susceptibility to infection (1, 10, 11). This partly depends upon the aggressiveness of the tumor and the degree of the hypercortisolemia. Laboratory evaluation may show evidence of glucose intolerance and hypokalemia. Due to the wide range of possible presenting symptoms, diagnosis of a unifying syndrome can often be challenging.

Once EAS is suspected, a number of diagnostic modalities can be used to confirm hypercortisolism including measuring urinary-free cortisol, the low-dose or overnight dexamethasone suppression test and late night salivary cortisol test. In most instances, urinary-free cortisol will be elevated, serum cortisol will not be suppressed with low-dose dexamethasone, and there will be elevation of salivary cortisol and a lack of a physiological circadian rhythm. Differentiating an ectopic source of ACTH from a central source arising from a pituitary adenoma can be accomplished with a high-dose dexamethasone suppression test, in which cortisol and ACTH tend to be non-suppressible (12). A corticotropin-releasing hormone (CRH) test can also be done to confirm the diagnosis of EAS, in which there tends to be a blunted or absent ACTH and cortisol response (1). Absolute levels of ACTH may also be helpful in distinguishing EAS from Cushing's disease if the ACTH level exceeds 200 ng/l, but considerable overlap exists. Once a neoplastic source is identified by CT scan, needle biopsy with hematoxylin and eosin staining, venous sampling, and testing for immunoreactivity for ACTH can help confirm the diagnosis. Such p-NETs causing EAS are also commonly positive for gastrin, pro-opriomelanocortin (POMC), and chromogranin A, a neuroendocrine secretory granule marker (1). ACTH levels can be measured with an immunoradiometric assay and POMC and somatostatin receptor (SSTR) expression can be confirmed by immunohistochemistry and/or reverse transcriptase-polymerase chain reaction (10). CT can miss smaller lesions, in which case, scintigraphy has been successfully used as an alternative (10). The neoplastic lesions must be tested for the presence of SSTR's because the presence or absence can drive treatment management and identification of metastases. Indium-111 penetreotide (Octreoscan), an analog of somatostatin, binds to SSTRs, especially SSTR2 and SSTR5, and as a result, can be used to identify gastroenteropancreatic NETs with postive SSTR expression (10).

Treatment goals are to reduce the size of single or multiple lesions, prevent further growth of each lesion, and ideally control and reduce the production of ACTH and cortisol (1, 10). Reducing cortisol levels is crucial in order to prevent potential sequelae of hypercortisolemia, which include but are not limited to the development of diabetes mellitus, hypertension, the metabolic syndrome, gastric ulcers, fractures, a hypercoaguable state with the risk for pulmonary embolus, psychiatric disorders, and infections. Metyrapone, an inhibitor of cortisol synthesis, can be an effective first line therapy and quickly reduces cortisol levels, but has limited availability in some countries including the United States. Etomidate, a hypnotic, rapidly lowers cortisol levels and is of particular utility for individuals unable to take oral medication or who present with sepsis. This medication must be given intravenously in an intensive care setting. Mifepristone, a progesterone and glucocorticoid receptor antagonist, would also be expected to have rapid effects to control symptoms associated with severe hypercortisolemia, but there is limited experience with this drug and it may worsen hypokalemia. Alternative therapies include ketoconazole, an anti-fungal agent that inhibits cortisol production, but several weeks are necessary to achieve full control. For tumors expressing SSTR-2 and -5, the somatostatin analogs, octreotide and lanreotide, may also be effective by reducing ectopic ACTH production while concurrently stabilize the growth of the tumor. SSTR-2 is primarily responsible for the inhibitory effects of hormone secretion, whereas SSTR-5 mediates induction of apoptosis and suppression of tumor growth (13). Fortunately, 80% of islet cell tumors express SSTRs, making treatment with octreotide highly successful (14), stabilizing 36.5% of metastatic gastroenteropancreatic tumors for a minimum of 12 months (15). High-dose octreotide (300 μg daily) followed by 100 μg daily dosing, has been shown to successfully suppress ACTH to <10 μg/ml. In patients resistant to octreotide or lanreotide, pasireotide may be considered. Pasireotide binds to SSTRs 1, 2, 3 and 5, and has been shown in a multicenter phase II study to be effective in the treatment of advanced NET (16). In the presence of high metastatic burden, transarterial chemoembolization (TACE), with cisplatin at 100 mg with epirubicin hydrochloride at 20-35 mg and lipiodol at 2-3.5 ml at intervals of 4-6 weeks (1), or alternating a two-drug regimen with docorubicin plus dacarbazine and streptozocin plus fluorouracil have been used (10, 17, 18). TACE is useful in reducing the tumor burden before surgical intervention is considered. A known complication of TACE is hepatic artery stenosis, which can then progress to collateral circulation, and can lead to the inability to use TACE further as a treatment option (10).

Other treatment modalities include the use of systemic chemotherapy and interferon (IFN). Various single and combinatory cytotoxic chemotherapeutic agents have been used in the treatment of pancreatic NET. Mechanisms of action stemmed from alkylation, platinum, and incorporation of pyrimidine analogs to interrupt DNA synthesis. Temozolomide has been evaluated in the setting of NET, particularly p-NETs. Efficacy had been prospectively validated by Kulke *et al.* and the reported response rates ranged from 24 to 45% (19). A retrospective analysis revealed a potential benefit with the addition of capecitabine (CAPTEM) where response rates were reported at 70% (20). Furthermore, a prospective trial evaluating safety and efficacy of CAPTEM was assessed by Fine *et al.* (8). The study reported response rates of 61% in 18 patients. The majority of patients (55%) were noted to have a partial response PFS at 14 months, and overall survival after the diagnosis of hepatic involvement was measured to be at 83 months. Overall, the study further validated that capecitabine, in combination with temozolomide, is efficacious and well tolerated in the setting of metastatic disease associated with neuroendocrine tumors of the gastroenteropancreatic tract.

Mammalian target of rapamycin (mTOR) inhibitors are also promising therapies for gastropancreatic NETs, due to the known dysregulation of the mTOR pathway present in these malignancies. Everoliumus, which was first approved for the treatment of p-NETs in 2011, has been shown to be an effective monotherapy regimen through the RAD001 in Advanced Neuroendocrine Tumors (RADIANT)-3 trial. Both, everolimus and temsirolimus, have been shown to produce a 11-month progression-free survival, compared to 4.6 months with placebo. In fact, through the synergistic relationship between mTOR and VEGFR inhibition, temsiroliums has been further shown to have an added benefit when combined with bevacizumab (21).

More recently, transcatheter radioembolization with yttrium-90 microspheres has been shown to be safe and effective in the treatment of unresectable metastatic neuroendocrine tumors (22-24). In a retrospective review involving 148 patients with unresectable neuroendocrine hepatic metastases who underwent yttrium-90 resin microsphere radioembolization, imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. No radiation-associated liver failure occurred. The median survival was 70 months (23).

Surgical resection or transplantation of affecting organs, primarily the liver, can be considered if there has been failure to respond to medical management. A meta-analysis of 103 patients with total hepatectomy and transplantation showed a 60% overall two-year survival rate and a 47% five-year survival rate, with a recurrence-free rate of 24% (25).

Conclusion

Due to the delay in symptom onset, varying differences in clinical presentation, and aggressive nature of ACTH-producing p-NETs, it is evident that rapid diagnosis and treatment start are the cornerstone of attaining a favorable prognosis. Although medical management is the primary mode of treatment, failure to respond can ultimately indicate the need for surgical resection. As with our patient, surgical resection of the primary tumor does not ensure that recurrence as metastatic disease will not occur. As a result, close follow-up with an endocrinologist and oncologist are essential.

Conflicts of Interest

None declared.

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