Ectopic Cushing Syndrome and Pancreatic Cancer: A Case Report

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**Abstract**

**OBJECTIVE:** Describe a rare case of ectopic Cushing syndrome associated with neuroendocrine pancreatic tumor.

**CASE:**
- 62-year-old female presented to her PCP because of dizziness and generalized weakness. Her BP was 180/60, and her physical exam was significant for +2 bilateral LE edema, very ruddy-looking complexion, significant RUQ abdominal tenderness, and proximal and distal muscles weakness. Labs revealed potassium 1.9, chloride 86, and HC03 >50. She was hospitalized for her electrolytes abnormalities and workup was initiated to rule in/out hyperaldosteronism versus Cushing syndrome. Aldosterone, renin activity, TSH, FT4, and ACTH levels were within normal limits. However, random cortisol was 46.6. Dexamethasone suppression test was abnormal with an cortisol level of 36.8. 24 hour cortisol was elevated at 336 consistent with ectopic Cushing.
- CT abdomen showed acute pancreatitis and multiple small liver lesions, but lipase and amylase were not markedly abnormal. Further evaluation with MRI abdomen showed poorly enhancing pancreatic mass measuring 1.4 cm concerning for adenocarcinoma with numerous small liver hypoenhancing lesions worrisome for metastases. CT guided biopsy of the liver lesions was performed and initial pathology was pancreatic adenocarcinoma. Since pancreatic adenocarcinoma rarely causes Cushing (only 1 case has been reported in the English literature), second opinion was sought and biopsy showed high grade large cell- type neuroendocrine pancreatic tumor. Patient refused any aggressive treatment and opted for hospice care. She expired soon after.

**DISCUSSION:**
- Many malignant tumors are capable of causing paraneoplastic syndromes, by producing a variety of substances whose biological activities are identical to various endocrine hormones. Adrenocortical hyperactivity is the most common endocrine derangement. Pancreatic tumors account for <1% of all cases of Cushing syndrome, and are usually very aggressive. Only 53 cases of ectopic Cushing associated with neuroendocrine pancreatic tumors have been identified thus far. Pancreatic neuroendocrine tumors should be considered during evaluation of ectopic Cushing.

**Cancer and Hypercortisolism**
- Two thirds of reported cases of endogenous hypercortisolism have been caused by pituitary tumor, with female to male ratio of 8:1, and usually occurs between the ages of 20 to 40.6
- Cortisol secreting tumors of the adrenal glands accounts for 15% of Cushing syndrome cases.5
- 15% of hypercortisolism is due to paraneoplastic syndrome.6
- The most common cause of ectopic Cushing paraneoplastic syndrome is oat cell carcinoma of the lung. It accounts for 60% of the cases, and occurs more frequent in men, between the age of 40 to 60 years old.
- Second most common cause is thymic tumors, which have been reported in 15% of the cases. Other sites of primary tumors include the pancreas, CNS, breast, thyroid, prostate and esophagus.
- Cushing syndrome develops insidiously, and patient could present with any of the following symptoms: weakness, easy bruising, moon face, reddish purple striae, peripheral edema, buffalo hump, HTN and emotional liability.
- Electrolyte disturbance specifically hypokalemia and alkalosis, is relatively common.

**Discussion**
- The pancreas has both endocrine and exocrine glands. The exocrine component (i.e. exocrine pancreas) produces enzymes that help break down carbohydrates, proteins and lipids in chyme. More than 95% of malignant neoplasms of the pancreas arise from the exocrine component.13 Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer, and it represents more than 80% of the cases of the exocrine pancreatic neoplasms.10
- Ectopic pancreatic carcinomas, the most common type of pancreatic neoplasms, are usually considered pure exocrine tumors. However, 43 to 67% of exocrine pancreatic carcinomas have been reported to contain endocrine (argyrophil) cells.13 Immunohistochemical techniques have identified immunoreactivity for various biochemical amines and peptides in these endocrine cells, e.g., 5-hydroxytryptamine, insulin, glucagon, gastric, somatostatin, and vasoactive intestinal peptide.13 However, typical syndromes related to high circulating levels of such substances are extremely rare.13 Besides, only 1 case of exocrine pancreatic carcinoma with Cushings symptoms attributable to hormonal hyper production (ACTH) has been reported by L. Gullo in 1992.
- The endocrine pancreas, on the other hand, is made up of cell clusters called islets of Langerhans. They are classified by their secretion to alpha cells which secrete glucagon, beta cells which secret insulin, delta cells that secretes somatostatin, and PP cells (gamma cells) which secretes pancreatic polypeptide.11 Endocrine pancreatic neoplasms are also known as islet cells tumors or pancreatic neuroendocrine tumors,12 and they do comprise no more than 5% of pancreatic neoplasms.9

**Neuroendocrine tumors of the pancreas**
- Peak incidence of occurrence is between age 40 and 69 years.
- 40% to 91% of pancreatic neuroendocrine tumors are nonfunctional.

- 22% of patients with neuroendocrine tumor of the pancreas have hormonal syndrome
  - 70% insulinomas – which are benign in 90% of the cases
  - 15% glucagonomas
  - 10% gastrinomas and somatostatinomas – which have 80-90% relative risk of metastases
  - About 7% cause ectopic cushing. Have the tendency to metastasize to regional lymph nodes and the liver in most cases and also often metastasize to the peritoneum, kidneys, thyroid gland and bone.
  - Also VIPoma, pancreatic polypeptidoma, and cholcystokininoma

- The major clinical symptoms associated with functional neuroendocrine tumors of the pancreas depend on the hormone secreted.
- Pancreatic tumors account for <1% of all cases of Cushing syndrome, and are usually very aggressive.6

**Conclusion**
- It is the clinical acumen that remains the most important diagnostic tool and it was the reason behind our success in accurately diagnosing our patient’s primary cancer. Understanding the pathophysiology and applying it to pathology and/or radiographic imaging reads are important in delineating the correct diagnosis. Knowing that pancreatic adenocarcinoma can rarely result in ectopic cushing syndrome, pathology was sent for a second opinion, and final pathology demonstrated neuroendocrine tumor of the pancreas. Pancreatic adenocarcinoma and neuroendocrine tumor of the pancreas have different treatment, medical management and prognosis. Thus having the correct diagnosis is essential. Pancreatic neuroendocrine tumors are rare cause of ectopic cushing’s. However, they should still be considered in the differential given its aggressiveness, and thus the importance of early diagnose.