incidence of gastrinomas is 0.5 to 2 per million population[1]. Although 17-30% of gastrinomas will stain positive for both gastrin and ACTH, the clinical manifestation of both ZES and Cushing's syndrome is rare. In a study by Maton et al., 3 of 59 patients (5%) with sporadic ZES (not MEN1) had Cushing's syndrome as well[2].

Clinical Case:

A 63yo woman with DM2 presented with persistent diarrhea for 2 years, and was diagnosed with ZES with a gastrin level of 1359 pg/mL (<100 pg/mL). A CT A/P showed a 3.8 cm pancreatic tail mass with multiple liver lesions. These lesions showed positive uptake on octreoscan, and a biopsy was positive a pancreatic neuroendocrine (NE) tumor. Her diarrhea was controlled with a PPI and no other intervention was made.

7 months later, she experienced severe worsening of her DM control despite aggressive medication titration. Due to new confusion and lethargy, she presented acutely to the ED. Labs showed metabolic alkalosis and profound hypokalemia with a CO2 38 mmol/L (22 - 31 mmol/L), venous pH 7.58 (7.32 - 7.42) and K 2.1 mmol/L (3.5 – 5.0 mmol/L). Her skin was diffusely hyperpigmented, and she had numerous cushingoid features on exam including supraclavicular fat pads, round face, thin skin and thin extremities. A subsequent cortisol level was found to be 125 mcg/dL (AM [6-10 am] 4.8 – 19.5 mcg/dL) with an ACTH of 1081 pg/mL (6-50 pg/mL).

She was not an optimal candidate for adrenalectomy given previous abdominal surgeries. After an octreotide drip (total 1475 mcg in 24 hrs) failed to reduce cortisol levels, metyrapone 250 mg q6h was started which led to an immediate and significant reduction in cortisol (209 to 38 mcg/dL), improved quality of life and significant reduction in her insulin and K supplementation requirement.

Conclusion:

We present a rare case of a dual gastrin and ACTH-secreting metastatic pancreatic NE cancer, in which overt ZES preceded the relatively abrupt onset of clinical Cushing's syndrome. Similar to Babu et al., the initial presentation was dominated by worsening DM control[3]. Despite the octreoscan positivity, cortisol production was not appreciably blocked by octreotide but was well controlled by metyrapone.

As seen in other cases, we again highlight the pluripotency of NE tumors and the ability to change hormone production. We also present the unique circumstance this patient faced for treatment options as she was not an optimal candidate for surgery.

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Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Protein Induced Pancreatic Hormone Secretion Is Modulated by Vagal CaSR

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The existence of a vago-vagal entero-pancreatic pathway, where sensory information from the gut can signal via vagal afferents to the brain to mediate changes in pancreatic function, has been recognised for over a century, and investigated extensively with regards to pancreatic exocrine secretions. However, the role of such pathways in pancreatic endocrine secretions has received less attention.

The secretion of insulin and glucagon in response to protein and amino acids is conserved across species. This effect is thought to promote amino acid uptake into tissues without concomitant hypoglycaemia. We found that the essential amino acid L-Phenylalanine potently stimulates glucagon secretion, even when administered directly into the gut at small doses unlikely to significantly raise systematic levels. Administration of L-Phenylalanine also increased neuronal activation in the rat and mouse dorsal vagal complex, the central nervous system region directly innervated by vagal afferents.

L-Phenylalanine modulates the activity of the calcium sensing receptor (CaSR), a nutrient sensor more commonly known for its role in calcium homeostasis, but which is thought to also act as a sensor of aromatic amino acids. Interestingly, the CaSR is one of the few nutrient sensors expressed in vagal afferents and *in vitro* calcium imaging revealed CaSR synthetic agonists activate subpopulations of vagal afferents.

The role of CaSR *in vivo* was investigated further by selectively knocking down the CaSR in vagal afferents. Briefly, CaSR floxed mice were bilaterally injected directly into the nodose ganglion, where the cell bodies of vagal afferents are located, with a cre expressing adeno-associated virus. CaSR knockdown did not interfere with normal food intake, nor the vagal-dependent anorectic effects of cholecystokinin, or of L-Phenylalanine. However, it did blunt protein-induced glucagon secretion, suggesting involvement of the CaSR in the vagus nerve in protein sensing and glucose homeostasis.

Future studies are required to determine the importance of vagal CaSR in protein induced pancreatic endocrine secretions, and the possibility of exploiting this circuit to develop new anti-diabetic therapies.