Ectopic Cushing's Syndrome and Severe Hypocalcemia due to Medullary Thyroid Cancer Responsive to Selpercatinib

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Introduction

- Medullary thyroid cancer (MTC) accounts for 1-2% of thyroid carcinomas in the United States. RET mutations (germline or somatic) occur in 70% of MTC.
- Unlike other thyroid carcinomas, MTC is a neuroendocrine tumor of the C-cells of the thyroid that secretes calcitonin (Ctn) and carcinoembryonic antigen (CEA).
- MTC can occasionally secrete hormones other than Ctn such as ACTH causing ectopic Cushing's syndrome (CS).
- Ectopic CS is characterized by rapid progression of disease leading to hyperglycemia and hypokalemia. However, hypocalcemia is rarely seen.
- Initiation of selpercatinib, a highly selective RET kinase inhibitor, greatly improved hypocalcemia and ectopic CS in this case.

Initial Presentation

2018: Initial Diagnosis

- A 39-year-old man was diagnosed with MTC during evaluation of 3cm painless neck mass and diarrhea. US FNA positive for neuroendocrine tumor. Underwent total thyroidectomy with bilateral neck dissection. Pathology confirmed diagnosis of MTC with positive for RET 918T c.2753T>C variant.

2019: Initial Follow-up

- Ctn and CEA started to gradually rise (see table below). CT scan showed progression of disease locally and enlarged retrocaval lymphadenopathy.

2020: Development of Cushing's Syndrome

- Patient gained 10 lbs over the course of one month, noted new stretch marks on abdomen, and difficulty walking due to proximal weakness and lower extremity edema. Also reported mental fogginess, perioral numbness, and tingling in hands and feet.
- He was hospitalized 3 times for management of severe hypocalcemia. He was diagnosed with new onset diabetes requiring insulin therapy (HbA1c 8.3%).
- He was ultimately transferred to our institution, and was lethargic, had multiple ecchymosis on abdomen and extremities, purplish wide striae on abdomen, peripheral edema and proximal myopathy. Laboratory evaluation revealed Ca 5.4 mg/dL, alb 3 g/dL.
- **Serum cortisol** measured at 9:30 pm was **136 ug/dL, ACTH 1,145 pg/mL and 24-h UFC 27,629 ug/d** suggesting CS due to ectopic ACTH production. Calcitonin and CEA were 18,687 pg/mL and 3,766 ng/mL.

Initial Laboratory Evaluation

Date	Ctn Pg/mL	CEA ng/mL	Ca mg/dL (alb 3 g/dL)	K mmol/L	Glu mg/dL
09/2018	5,466	657	7.9		
05/2019	104	12.3	9	4	
09/2019	248	27.7			
10/2019	646	34.7	8.7	4.1	95
1/24/20	18,687		6.7	2.9	193
2/13/20	19,080		5.9	3.6	195
***2/24/20**	**15,861**	**3,766**	**5.4**	**2.6**	**284**

Additional labs

iPTH: 1.4 pmol/L (L)
Phosp: 2.6 mg/dL
25OH Vit D: 23

Cortisol PM136 ug/dL
ACTH 1,145 pg/mL
24h UFC 27,629 ug/d

TSH 0.94 mIU/L
Plasma MN < 25
Plasma NMN: <25

Initial Imaging

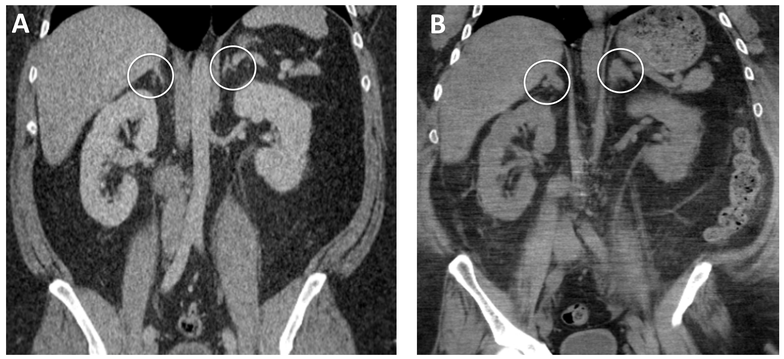
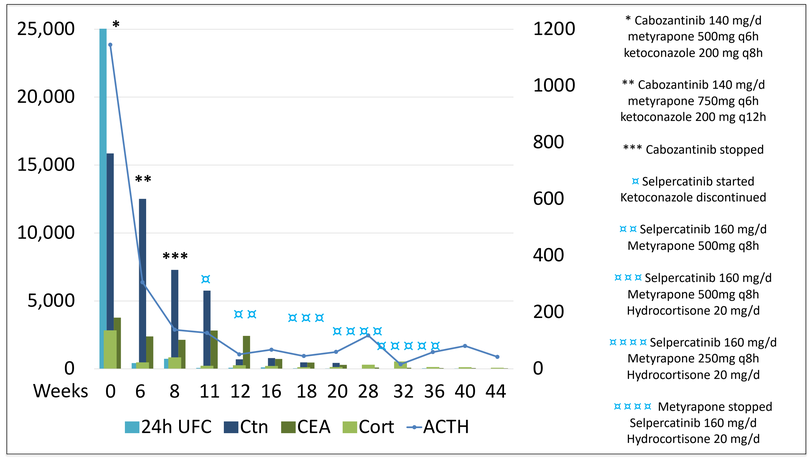


Figure 1. Computed tomography of the abdomen/pelvis without contrast: Panel A (May 2019) and Panel B (Feb 2020): numerous large hepatic tumors (not visible in this view). There is new bilateral adrenal hyperplasia. Adrenal glands in white circles.

Clinical Course: Hospitalization and Follow-up

- Patient required calcium drip up to 1.5mg/kg/hr for about 1 week, in addition to high doses of oral calcium and calcitriol. Started ketoconazole, metyrapone, and cabozantinib
- Hospital course was complicated by infections and recurrent scrotal bleeding, so he was switched to selpercatinib 160 mg daily. Two days after starting selpercatinib, ketoconazole was discontinued, and metyrapone was gradually reduced. Hydrocortisone 20 mg daily was added 2 months later.
- Hypercortisolism continued to improve (24h UFC 10ug/d) as well as calcitonin and CEA levels (149 pg/mL and CEA 97.8 ng/mL, respectively). Metyrapone was discontinued 6 months after initiation of selpercatinib.
- Similarly, refractory hypocalcemia greatly improved, last Ca was 8 mg/dL on elemental Ca 240 mg/d. He made significant clinical gains and returned home from rehab.
- Due to concern about long term effectiveness of selpercatinib, it was recommended to proceed with bilateral adrenalectomy.

Biochemical Response



Follow-up Imaging

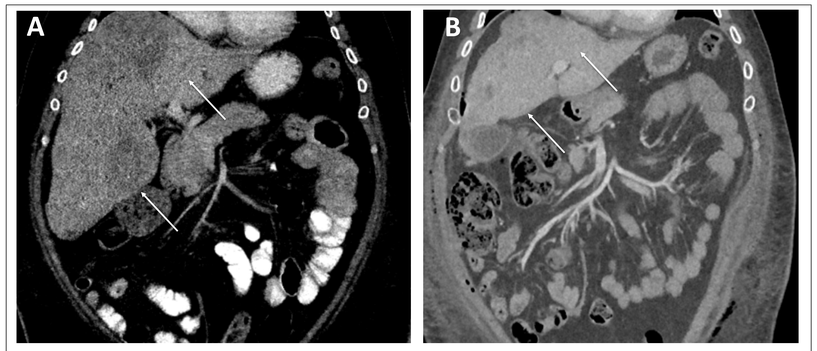


Figure 2. Computed tomography of the abdomen/pelvis with contrast: Panel A (May 2020) and Panel B (Feb 2021): interval improvement in hepatic metastatic lesions (in white arrows) 9 months after treatment with selpercatinib.

Discussion

- Hypocalcemia is rarely described as a complication in patients with CS. Our patient had underlying hypoparathyroidism and vitamin D deficiency; however, hypocalcemia was initially refractory to high doses of calcium and calcitriol and only improved with treatment of CS.
- We hypothesize his hypercortisolemia reduced activation of 25 to 1,25 D (reducing gastrointestinal absorption of calcium), and also caused hypercalciuria. These deleterious effects of severe hypercortisolemia combined with underlying hypoparathyroidism led to severe and refractory hypocalcemia requiring repeated admissions, which only improved once his ectopic CS due to MTC was recognized and controlled.
- RET mutations occur in 70% cases of MTC, which is target of recently approved kinase inhibitors. Multitargeted kinase inhibitors such as cabozantinib and vandetanib have been approved for treatment of MTC, with a response rate that ranges from 12 to 65%.
- Prior case reports have been published about reversal of CS by vandetanib. However, only one case has been reported about resolution of CS with selpercatinib.
- The highly selective RET kinase inhibitor, selpercatinib, was recently approved by the FDA in May 2020. In the case of our patient, it induced a rapid decline in calcitonin, CEA and ACTH levels which enabled control of hypercortisolemia and its complications.
- Although patient showed an excellent response to selpercatinib and achieved remission of CS , it is not known the durability of this effect. Therefore, it was decided to proceed with bilateral adrenalectomy to prevent future recurrence of CS.

References

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