Successful resolution of Cushing syndrome due to ectopic ACTH syndrome in metastatic medullary thyroid carcinoma during treatment with selpercatinib (LOXO-292), a novel highly selective RET inhibitor

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BACKGROUND
- Medullary Thyroid Cancer (MTC) is rare neuroendocrine tumor representing less than 5% of all histological variants of thyroid cancer.
- Hereditary MTC (25% of all cases) occurs secondary to a germline mutation of the RETarranged during Transfection proto-oncogene (RET); at least half of sporadic MTC cases harbor a somatic RET mutation.
- Ectopic Cushing syndrome occurs in <1% of MTC cases, although rare this manifestation presents a poor prognosis with mortality rate of 50%.
- This is the first case demonstrating a highly selective RET inhibitor therapy, specifically selpercatinib (LOXO-292), inducing total remission of ectopic Cushing syndrome secondary to advanced metastatic MTC.

CASE FINDINGS
- 52-year-old male diagnosed with multiple endocrine neoplasia IIa (2013) given positive family history of MTC and a germline RET C618R mutation.
- Total thyroidectomy, bilateral central and lateral neck dissections performed, revealed multifocal MTC, largest focus 4.8 cm on right with 35/91 metastatic foci, nodal extrathyroidal extension, and substantial areas of extranodal extension.
- Given pre-operative calcitonin 30,000 pg/mL and CEA 805 ng/mL, initial staging revealed metastatic sites including: mediastinal lymphadenopathy, liver and vertebral spine.
- In 2016, systemic therapy with vandetanib was initiated for progression.

CASE FINDINGS
- June 2018: hospitalization due to severe hypokalemia.
- Random cortisol was 69 mcg/dL and adrenocorticotropic hormone was ACTH 244 pg/mL confirming ectopic Cushing syndrome.
- Metyrapone therapy was initiated for hypercortisolism, titrated to 500 mg orally three times a day with concomitant dexamethasone to prevent adrenal insufficiency.
- Despite therapy for hypercortisolism, patient clinical status continued worsening & complicated with Pneumocystis jiroveci pneumonia requiring prolonged hospitalization.
- Patient was enrolled on compassionate single patient protocol of selpercatinib (LOXO-292) 80 mg orally twice a day titrated to 120 mg twice a day by 8 weeks.

CASE FINDINGS
- Patient experienced complete resolution of symptoms of Cushing syndrome, without further recurrence of hypercortisolism state.
- Patient has maintained a stable biochemical response & confirmed partial response by RECIST 1.1.

DISCUSSION/CONCLUSIONS
- This case presents a clinical scenario of advanced metastatic RET-mutated medullary thyroid cancer despite two prior lines of therapy with multitarget kinase inhibitor and life-threatening complication of ectopic Cushing refractory to high dose metyrapone.
- Highly selective RET inhibitor provided complete remission of hypercortisolism state and sustained tumor burden control.
- Prior reported cases of Cushing Cushing syndrome to MTC demonstrating response to multitarget inhibitor have the limitation of the multi-receptor targeting of these medications.
- Several possible hypotheses are raised as potential mechanisms including:
  a) Mitogen associated protein kinases pathways as regulators of ACTH secretion given reports of EGFR signaling induced expression of proopiomelanocortin (POMC), the precursor of ACTH.
  b) ACTH induced cyclic AMP elevation and protein kinase A activation on adrenal cells affecting steroidogenesis.
  c) Direct adrenal action of kinase inhibitor via 21-hydroxylase and 17-hydroxylase inhibition as well as highly selective RET inhibitor regulation of glucocorticoid receptors.
- Selpercatinib is an effective and tolerable highly selective RET inhibitor that induced rapid ACTH decline in ectopic Cushing syndrome to metastatic MTC. Our case suggests the probability of RET activation as a direct regulator of ACTH secretion which can be effectively targeted with RET selective treatment in cases of advanced MTC with paraneoplastic hypercortisolism.

CASE FINDINGS
- Highly selective RET inhibitor provided complete remission of hypercortisolism state and sustained tumor burden control.

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