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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 REarranged 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 nodes, focal 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.
- After 22 months of vandetanib therapy, due to radiographic progression and rising tumor markers, the treatment was switched to cabozantinib.
- In April 2018, T2-T5 vertebral spine metastases were treated with palliative radiation (external beam radiotherapy-2000 cGy/5 fractions).
- Cabozantinib therapy was discontinued in May 2018 after dose reductions due to adverse events (worsening hypertension & abdominal pain).
- Meanwhile, patient was progressively developing fatigue, weight loss, advancing proximal muscle weakness, polyuria, facial and distal extremity paresthesia, facial spasms, and hoarseness.

CASE FINDINGS

- June 2018: hospitalization due to severe hypokalemia.
- Random cortisol was 69 mcg/dL and adrenocorticotropic hormone was ACTH 245 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 jirovecci* 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.

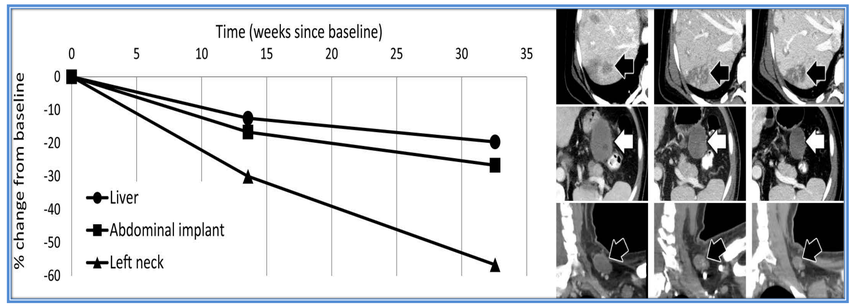

Figure 1. Tumor response post-highly selective RET inhibitor initiation.
Left panel- Percent of change from baseline at measurable sites of disease-Of note, left neck disease demonstrated a partial response (≥30% decrease in tumor size) by RECIST 1.1 at less than 15 weeks of therapy.
Right Panel- From top to bottom, metastatic liver, abdomen and left neck lesions.

	Duration of Selpercatinib Treatment					
	Baseline	1 Month	2 Months	3 Months	5 Months	10 Months
Calcitonin (pg/mL)	93,526	1,956	1,233	1,041	623.6	623.8
CEA (ng/mL)	612.9	210.4	160.2	106	82.2	86.5
ACTH (pg/mL)	141	33	5	81	17	60
Cortisol (mcg/dL)	8.28*	0.53**	<0.1***	4.84	1.49	6.08

Table 1. Biochemical response of selpercatinib therapy
* On metyrapone 1,000 mg four times daily and dexamethasone
** Metyrapone dose decreased to 1,000 mg twice a day
*** Metyrapone discontinued

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 multikinase 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 ectopic Cushing secondary to MTC demonstrating response to multikinase 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 secondary 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.

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