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An Unusual Case of Sporadic Metastatic Medullary Thyroid Cancer Without a Primary Tumor Presenting with Paraneoplastic Cushing's Syndrome

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Introduction: Medullary thyroid carcinoma (MTC) accounts for 5-10% of all thyroid cancers and up to 30% of MTCs are hereditary. Only 0.6% of MTCs are associated with a paraneoplastic ACTH-dependent Cushing's syndrome (CS) (PMID: 16029131). Even rarer are MTCs without a primary intra-thyroidal tumor. Here we describe a patient with metastatic MTC without a known primary intrathyroidal tumor presenting with paraneoplastic ACTH-dependent CS.

Clinical Case: A 47-year-old Ukrainian man was referred to our center for management of metastatic MTC. During evaluation of refractory diarrhea two years earlier, an elevated serum calcitonin (1758 pg/mL, normal: <11.5) led to the diagnosis. Thyroid ultrasound revealed a normal thyroid with bulky cervical lymphadenopathy. Cervical lymph node biopsy revealed metastatic MTC with positive calcitonin, synaptophysin, and chromogranin-A on immunohistochemistry (IHC) and RET protooncogene M918T pathogenic variant on molecular testing. Germline testing for RET pathogenic variants was negative. Prior to referral, the patient was on octreotide to control diarrhea and vandetanib for a few months, but they were discontinued due to financial stress. At our center, patient complained of 4-6 watery bowel movements daily. Physical examination

revealed facial plethora, dorsocervical fat pad, central adiposity, wide purple striae, and pustular acne on the chest wall and proximal muscle weakness.

Biochemical testing revealed elevated serum calcitonin (158,535 pg/mL, normal: <14.3), carcinoembryonic antigen (3,634 ng/mL, normal: 0.8–6.2), and chromogranin-A (5504 ng/mL, normal<93) levels. Morning serum cortisol (40.4 mcg/dL, normal: 3.7–19.4), and plasma ACTH (116.0 pg/mL, normal: 5.0-46.0) levels were elevated, along with markedly elevated 24-hour urine free cortisol levels (12,460.8 mcg/24-hour, normal: 35-45.0), consistent with ACTH-dependent Cushing's syndrome. Further IHC testing of the tumor biopsy sample revealed mild ACTH positivity. A pituitary MRI was normal. Stool osmolality studies showed a secretory diarrhea pattern. Computed tomography (CT) of neck and torso demonstrated bulky cervical, retroperitoneal, and inguinal lymphadenopathy, and extensive liver metastasis, all of which were strongly avid on an 18-fluorodeoxyglucose positron emission tomography CT scan, but poorly avid on a gallium-68 DOTATATE scan. Sodium fluoride bone scan revealed multiple osseous metastases in the spine, ribs, pelvis, and in the right femoral shaft. An adrenal CT scan revealed bilateral adrenal hyperplasia.

The patient was unfortunately not eligible for any ongoing local clinical trials on RET-mutated cancer therapies. After extensive discussion with the patient, a palliative approach was pursued. The cervical lymphadenopathy and right femoral shaft metastasis were treated with external beam radiation. Diarrhea was controlled with loperamide. Cushing's syndrome was initially managed with metyrapone and ketoconazole, followed by bilateral adrenalectomy and hydrocortisone and fludrocortisone replacement.

Conclusion: Sporadic metastatic MTC can rarely present without an intrathyroidal primary tumor and may originate from ectopic C-cells. Paraneoplastic syndromes such as Cushing's syndrome can be observed in MTC due to ectopic-ACTH production.

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