tests were normal. Significant labs include: serum glucose 17 mg/dl, C-peptide <0.10 ng/ml (n: 1-4 ng/ml), serum insulin <1.6 Uu/ml (n: <20 Uu/ml), beta-hydroxybutyrate <0.2 mmol/L (n: <0.3), cortisol 10.8 ug/dl(n: 5-15 ug/dl) glucagon 6 pg/ml(ref 8-57 pg/ml), insulin-like growth factor-1 (IGF 1) 20 ng/ml (n: 52-328), and IGF-2 level 380 ng/ml (267-616 ng/ml), improvement in blood glucose from 46 to 111 mg/dl after 1-gram glucagon administration. The IGF-2/IGF-1 ratio of 19 confirmed our clinical suspicion of non-islet cell tumor hypoglycemia (NICTH). He was started on prednisone 20 mg twice daily with marked improvement in hypoglycemia.
Conclusion: NICTH is a rare cause of hypoglycemia and should be considered in the differential while evaluating hypoglycemia in malignancy. For diagnosing NICTH, assays for big IGF-II are not commercially available. However, the IGF-II:IGF-I ratio is considered to be a surrogate marker of big IGFII concentration. The normal ratio is 3 and ratio >10 is diagnostic of NICTH. In cases like ours where tumor resection is not possible, glucocorticoids are most effective in management of hypoglycemia by inhibiting big IGF2 production and stimulating gluconeogenesis.

Tumor Biology
TUMOR BIOLOGY CASE REPORTS

A Case of Paraneoplastic Cushing's Syndrome in Recurrent Squamous Cell Carcinoma

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Background: Ectopic production of ACTH causing Cushing's syndrome (CS) is rare but has been well described in association with bronchial carcinoids, thymomas, pancreatic malignancies, and small cell lung carcinomas. We report a rare case of CS caused by ACTH-producing non-small cell carcinoma.
Clinical Case: A 71 year-old man with a history of squamous cell carcinoma of the lung (T2bN1M0) 10 years prior who underwent lobectomy and adjunctive chemotherapy, presented with a new cough, weight loss, and bilateral lower extremity edema. He was also noted to have significant fatigue, hypertension, symptomatic hyperglycemia, and hypokalemia. CT chest revealed a large right perihilar mass with mediastinal adenopathy and numerous hepatic lesions.
A biopsy of the liver lesions revealed a poorly differentiated carcinoma with neuroendocrine features strongly positive for AE1/3 with focal p40+, CK7, synaptophysin, chromogranin, and TTF1. It was negative for p63, CK5/6, CDX2, CK20, and GATA3. The morphology and immunohistochemical staining favored a squamous primary. Unfortunately, there was insufficient tissue sample to stain for ACTH. Biochemical evaluation revealed: post-1 mg dexamethasone serum cortisol 74.8 µg/dL (N < 1.8 µg/dL), 24 hr urine free cortisol 2987 µg/g creatinine (normal: < 32 µg/g creatinine), and ACTH 170 pg/mL (N < 47 pg/mL). Other notable findings at presentation were potassium 2.8 mmol/L (N: 3.7-5.1 mmol/L) and glucose 371 mg/dL (N: 74-99 mg/dL). MRI brain revealed focal pituitary infundibular thickening up to 6 mm in diameter and an enlargement of the pituitary gland concerning for metastasis. The patient's clinical course was complicated by persistent hypokalemia and hyperglycemia which were treated with spironolactone 100 mg twice a day and insulin therapy, respectively. Ketoconazole 100 mg twice a day was initiated for the hypercortisolemia; etoposide, carboplatin, and atezolizumab were started for the neuroendocrine tumor. The patient expired due to sepsis one month after the diagnosis of Cushing's syndrome. **Conclusion:** We report a rare case of paraneoplastic Cushing's syndrome due to poorly differentiated neuroendocrine tumor with a squamous cell carcinoma primary. ACTH producing non-small cell carcinomas have been seldom reported in the literature. Although we were unable to provide ACTH staining on pathology, the existence of an obvious neuroendocrine tumor, marked elevation in ACTH, and an MRI which was negative for a pituitary adenoma, strongly suggests paraneoplastic Cushing's syndrome.

Tumor Biology
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A Case of Paraneoplastic Hypoglycemia From Squamous Cell Carcinoma of Undetermined Primary

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Case: A 57 year old man with squamous cell carcinoma (SCC) of the tongue with complete response to chemoradiation was found unresponsive with a reading of "low" by a POC glucometer. He was treated with an IV dextrose bolus but had recurrent hypoglycemia requiring a continuous dextrose infusion. He was diagnosed with COVID-19 pneumonia, acute hepatitis (elevated liver enzymes), and acute kidney injury (elevated serum creatinine 1.2 mg/dL). Other labs: elevated TSH 8.44 uIU/mL, normal AM cortisol 16.4 ug/dl. A 5.1 cm mass was discovered in the left lung with bilateral nodules, biopsi revealed SCC of unclear origin (either lung or metastatic disease from prior tongue cancer). He was malnourished from prior cancer related dysphagia and nutritional supplements were added. Despite this and improvement in liver and kidney function, he had persistent hypoglycemia. He became hypoglycemic within 4-hrs while performing a 72-hr fast with labs: serum glucose 45 mg/dL, insulin &lt 2 uU/mL, c-peptide &lt 0.1 ng/mL, proinsulin &lt 4 pmol/L, beta hydroxybutyrate 0.17 mmol/L, IGF1 &lt 16 ng/mL (ref: 50 - 317), IGF2 147 ng/mL (ref: 267-616), negative hypoglycemia panel and insulin antibody. This was consistent with a paraneoplastic hypoglycemia known as non-islet cell tumor hypoglycemia (NICTH). To discontinue the dextrose infusion, he was started on prednisone 20 mg daily titrated up to 60 mg daily, intermittent tube feeds and palliative chemotherapy. With this, hypoglycemia improved, and the dextrose infusion was discontinued. Unfortunately, he had ischemic bowel perforation leading to cardiac arrest and death. **Discussion:** Our patient had NICTH as suggested by the 72-hr fast (non-insulin mediated hypoglycemia, IGF2/IG1 ratio &gt 10) and the presence of a tumor. It is mediated by tumor-produced IGF-2 causing

increased glucose utilization, decreased gluconeogenesis, glycogenolysis and ketogenesis. Curiously, IGF-2 may not be elevated if the tumor produces a partially processed "big IGF-2" for which there is no commercial assay. Instead, an IGF2/IGF1 ratio close to or more 10 is indicative of NICTH. Mesenchymal and hepatic tumors are the most common cause of this rare entity with an incidence of one per million people years. A literature search showed very few reports of SCC-mediated-NICTH, with one case of esophageal SCC. Our patients' primary tumor was undetermined (lung vs tongue) - but in either case this could be a novel association. A multidisciplinary approach is required centered around the tumor (surgery, chemotherapy, or radiation). High dose prednisone 30 to 60 mg daily can be used in the interim as it decreases IGF-2 but is not always successful. Recombinant hGH and glucagon are alternatives or can be combined with steroids. In summary IGF2/IGF1 ratio should be calculated, palliative tumor directed therapy should be initiated with prednisone and supplemental nutrition as adjuncts.

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A Rare Cause of Recurrent Hypoglycemia - The "Big-IGF-II" Factor

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Introduction: Hormone secreting tumors are a rare cause of hypoglycemia. Here we present an interesting case of paraneoplastic phenomenon resulting in a non-islet cell tumor causing hypoglycemia (NICTH) from a solitary fibrous tumor (SFT). **Clinical Case:** An 83-year-old female with a history of hypertension presented with recurrent episodes of lightheadedness and falls for one month. Review of systems was negative except for insignificant weight loss. Her vital signs and physical examination were unremarkable. Only significant finding on initial blood work was a blood glucose level of 30 mg/dL (n: >70mg/dL). Additional work-up of hypoglycemia revealed a low serum free insulin level 0.6 IU/mL (n:1.5 - 14.9 IU/mL), low proinsulin <4 pmol/L (n: <18.8 pmol/L), low C-peptide level 0.14 ng/mL (n: 0.80-3.85 ng/mL), low serum insulin-like growth factor-I (IGF-I) 33 ng/ml (n:34-246 ng/ml) and elevated IGF-II levels 370 ng/mL (n:47-350 ng/mL). Blood sulfonylurea and insulin antibodies screen were negative, ACTH and morning cortisol levels were within normal limits. A CT scan of chest, abdomen and pelvis for neoplastic workup demonstrated a large heterogeneous mass within the lower lobe of the right lung. A CT-guided biopsy disclosed spindle cell neoplasm, positive for signal transducer and activator of transcription-6 (STAT6) and CD34. Reverse transcription-polymerase chain reaction (RT-PCR) confirmed the NGFI-A binding protein 2 (NAB2) and STAT6 fusion which is specific for solitary fibrous tumor (SFT). She underwent surgical resection of the thoracic mass which resulted in complete resolution of her symptoms. **Clinical Lessons:** NICTH is a paraneoplastic syndrome associated with various benign and malignant tumors including SFT, hemangiopericytoma and metastatic hepatocellular carcinoma to name a few. Our case is an example of NICTH associated with SFT called Doege-Potter syndrome. The prevalence of hypoglycemia is seen in less than 5% of patients with SFT. It is often secondary to ectopic overexpression of unprocessed precursor 'big' IGF-II molecule, which binds to IGF-I receptor, resulting in tumorigenesis. An IGF-II/IGF-1 ratio is a sensitive marker and a value of more than 10 suggests excess production of IGF-II and is likely the cause of NICTH. Physicians should be cognizant of NICTH, especially in non-diabetic, otherwise healthy individuals in whom preliminary workup for hypoglycemia is negative and should look to identify any potential tumor as the likely cause. Surgical treatment is often the only curative option. Frequent meals, dextrose infusion, glucagon and growth hormone are bridging modalities until definitive surgical treatment.

Tumor Biology

TUMOR BIOLOGY CASE REPORTS

ACTH Producing Mediastinal Tumor - Multidisciplinary Approach

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Introduction: Ectopic ACTH syndrome is rare but is frequently a severe condition because of the intensity of the hypercortisolism. Patient management is complex and demands both strategies: the diagnosis and treatment of Cushing syndrome, and the specific management of neuroendocrine tumors. Therefore, management should be performed ideally by experienced endocrinology teams in collaboration with surgeons, oncologists, nuclear medicine, specialized hormonal laboratory and modern imaging platforms.
Clinical Case: Female patient, born in 2000, at the age of 15 was diagnosed with Cushing's syndrome secondary to ACTH secretion by mediastinal tumor. At diagnosis, ACTH 1152pg/ml was found (reference value <46pg/ml). Turkish seat resonance was normal, and chest tomography described a 4.5x3.6x3.8cm mediastinal lesion. Underwent a mediastinal surgical approach in 2015, with clinical and laboratory remission of hypercortisolism. The analysis of the lesion revealed a well-differentiated neuroendocrine carcinoma, with Ki67 5%. Progression of the mediastinal lesion was observed, without an exuberant clinic or laboratory, and a new surgery was performed in 2017, with a remaining macroscopic tumor, due to technical difficulties in resection due to contact with vascular structures. The immunohistochemistry of the resected lesion in this approach showed Ki67 30%, which reflects loss of differentiation. Octreoscan was performed, with no uptake. She evolved without exuberant Cushing's syndrome until May 2019, when the clinical condition decompensated due to hypercortisolism, and was submitted to a new hospitalization. She was assisted by the thoracic surgery and oncology teams. From this moment a follow-up with endocrinology team started. Ketoconazole was introduced and PET-DOTATOC was requested. She underwent chemotherapy