She had initially managed her diabetes with metformin but stopped taking the medication due to increasingly frequent episodes of hypoglycemia. Significant labs during the hospitalization include blood glucose <20 mg/dL, insulin 75.9 IU/mL (2.6-21.9 IU/mL) and C-peptide 57.7 ng/mL (1.1-4.4 ng/mL). Her symptoms persisted despite dextrose supplementation. Abdominal and Pelvic CT showed proximal small bowel obstruction and sclerosing mesenteritis with a calcified lymph node but no pancreatic mass. A diagnostic laparoscopy was performed, showing 18 inches of small bowel with malignant appearing masses that were adherent to the mesentery. A 21.0 cm segment of jejunum was resected. There were at least 30, variably sized masses throughout the bowel, involving the mucosa, submucosa, muscularis propria and subserosal fat; along with lymphatic, venous, and perineural space tumor permeation, and metastases involving multiple regional lymph nodes. The tumors ranged in size from 0.5 up to 1.5 cm. They showed well-differentiated nuclear morphology, a mitotic count of 0 per 80 high power fields, and a Ki-67 proliferation index of 1%, indicative of a G1 NET. Immunohistochemical stains confirmed neuroendocrine differentiation with positive staining for chromogranin, synaptophysin, and INSM1 (insulinoma-associated protein 1) transcription factor, while insulin staining was negative. The patient was diagnosed with a pT3N1, G1, ectopic insulin-secreting neuroendocrine tumor of small bowel origin. She was started on diazoxide with significant improvement in her hypoglycemia.

Conclusion: Insulin production by non-pancreatic tumors is extremely rare. Clinical, laboratory, and immunohistochemical tumor findings in this case support ectopic insulin production by a well-differentiated neuroendocrine tumor of small bowel origin.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

A Blood-Based Polyamine Signature Associated With Disease Progression in Patients With Multiple Endocrine Neoplasia Type 1-Related Duodenopancreatic Neuroendocrine Tumors

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Background: Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare inherited autosomal dominant disease predisposing patients to endocrine tumors. MEN1 can be genetically diagnosed at an early age. Patients are prone to develop benign parathyroid tumors then multifocal duodenopancreatic neuroendocrine tumors (dpNETs), which have a penetrance of >80% by age 80. Although they can be identified at an early stage, preventive measures do not exist, and one fifth of patients develop distant metastases, which is the most significant cause of mortality. *Currently, no biomarkers can reliably predict which patients with MEN1-related dpNETs are at high risk of developing metastatic disease.* Polyamines are naturally occurring polycationic alkylamines that have been implicated to play functional roles in promoting neoplastic transformation and growth. We have previously demonstrated a plasma polyamine signature that associates with pancreatic cancer development and that also offers value for predicting future distant metastasis in patients with triple-negative breast cancer. We hypothesized that such a plasma polyamine signature may similarly associate with disease progression in subjects with MEN1-related dpNET.

Methods: As part of an international collaboration, we measured plasma polyamine levels using mass spectrometry from 14 MEN1 patients with distant metastatic dpNET (cases), 28 MEN1 patients with indolent dpNETs without distant metastases (control-1), and 14 MEN1 patients without dpNETs (control-2). Five circulating plasma polyamines were quantified in this initial test set. A combination rule was developed using logistic regression models. Findings were validated in an independent set of plasma from 6 cases and 22 controls (n=13 control-1 and n=9 control-2).

Results: Area under the Receiver Operating Characteristic Curve (AUC) of individual polyamines delineating cases from controls ranged from 0.50-0.75 in the test set. A polyamine signature consisting of 3 polyamines developed in the test set yielded an AUC of 0.84 (95% CI: 0.63-1.00) with 67% sensitivity at 95% specificity in the validation set for distinguishing cases from controls. The predictive performance of the polyamine signature for distinguishing cases from MEN1 patients with indolent dpNETS without distant metastasis or MEN1 patients without dpNETS in the validation set was 0.79 (95% CI: 0.53-1.00) and 0.91 (95% CI: 0.75-1.00) with respective resultant sensitivity at 95% specificity of 50% and 67%.

Conclusion: Our findings reveal a plasma polyamine signature associated with disease progression in subjects with MEN1-related dpNETs. This polyamine signature may provide a potential breakthrough for predicting progression and distant metastasis in MEN1 patients. Further prospective studies are warranted.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

A Frame-Shift for IGF-1R in Breast Cancer and Metastasis

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