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Background Classical heterozygous pathogenic variants of the lamin A/C (LMNA) gene cause familial partial lipodystrophy type 2 (FPLD2). However, recent reports indicate phenotypic heterogeneity among carriers of LMNA pathogenic variants, and a few patients have been associated with generalized fat loss. Clinical Case Here, we report a patient with lamin A specific pathogenic variant at exon 11 LMNA p.R582H present in homozygous state. Fat distribution was compared radiographically to a heterozygote LMNA p.R582H patient from another pedigree, female healthy control, a series of adult female subjects with congenital generalized lipodystrophy type 1 (CGL1 n = 9) and typical FPLD2 (n = 8). The whole body MRI of the index case confirmed near-total loss of subcutaneous adipose tissue with well-preserved fat in the retroorbital area, palms and soles, mons pubis, and external genital region. This pattern resembled the fat loss pattern observed in CGL1 with only one difference: strikingly more fat was observed around mons pubis and the genital region. Also, homozygous p.R582H LMNA variant was associated with lower leptin level and earlier onset of metabolic abnormalities compared to heterozygous p.R582H variant and typical FPLD2 cases. On the other hand, heterozygous LMNA p.R582H variant was associated with partial fat loss which was similar to typical FPLD2 but less severe than the patients with the hot-spot variants at position 482. Conclusions Our observations and radiological comparisons demonstrate a gene dosage effect of LMNA variants on the severity of fat loss and add to the body of evidence that there may be complex genotype-phenotype relationships in this interesting disease known as FPLD2. Although the pathological basis for fat loss is not well understood in patients harboring pathogenic variants in the LMNA gene, our observation suggests that genetic factors modulate the extent of fat loss in LMNA associated lipodystrophy.

Tumor Biology
ENDOCRINE NEOPLASIA CASE REPORTS II

Multiple Endocrine Neoplasia Type 1- A Clarion Call for Clarity
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A 35-year-old gentleman presented with epigastric pain and bilious emesis. He also endorsed urinary frequency, non-bloody diarrhea and diffuse bone pain. On physical examination he had epigastric tenderness and multiple hyperpigmented skin lesions. An abdominal computed tomography (CT) scan revealed multiple diverticula with peri-colonic fat stranding in the descending and sigmoid colon, concerning for diverticulitis. He was started on a course of metronidazole and ciprofloxacin. A 3.1 cm mass was incidentally noted in the uncinate process of the pancreas. Bilateral adrenal nodules were also appreciated. An endoscopic ultrasound (EUS) guided trans-gastric fine needle aspiration biopsy was performed, revealing a well differentiated pancreatic neuroendocrine tumor (pNET - pT3N1Mx, intermediate risk). Chromogranin A was elevated to 108 ng/ml (reference range <93 ng/ml). Serum and urine metanephrine, V-peptide, gastrin, glucagon and parathyroid hormone related peptide were all normal; indicating a nonfunctioning neuroendocrine tumor. He underwent a pancreatecoduodenectomy. Octreotide scan was unrevealing for residual uptake. Adrenal biopsy revealed adrenal adenomas.

Three years later, he presented with severe abdominal pain and a new pancreatic mass was noted on CT. Chromogranin A was elevated to 227 ng/mL. EUS revealed a 0.35 cm mass in the bed of the pancreatic head, encasing the superior mesenteric artery. Pathology was positive for recurrence of the neuroendocrine tumor. He was hypercalcemic to 11.4 mg/dL and parathyroid hormone was elevated to 319 pg/mL. CT neck revealed a 0.1 cm nodule concerning for parathyroid adenoma. He underwent a subtotal parathyroidectomy.

Genetic testing confirmed Multiple Endocrine Neoplasia Type 1 (MEN1) with a heterozygous mutation of the menin1 gene.

MEN1 is a rare genetic syndrome with affected individuals at increased risk of developing pancreatic, pituitary, parathyroid gland and cutaneous tumors. With a kaleidoscope of presentations, clinicians must maintain a high index of suspicion for MEN1, particularly for cases with nonfunctioning pNETs which present insidiously and are the foremost cause of mortality in MEN1 patients. Further clarity is needed on MEN1 associated pNET prognostic risk stratification, surveillance and targeted immunochemotherapy. Timely and algorithmic screening for MEN 1 syndrome in patients with pancreatic incidentalomas is essential to improving patient outcomes.

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Thyroid
THYROID DISORDERS CASE REPORTS II

Transient Thyrotoxicosis with Immune Checkpoint Inhibitors Therapy: The Importance of Endocrine Evaluation
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Introduction
The immune checkpoint-blocking antibody nivolumab is recognized as having a crucial role in different malignancies by blocking programmed death-1 (PD-1) receptor immune cells. Besides its benefits, nivolumab may cause endocrine immuno-related adverse events (irAEs), including thyroid dysfunction (TD).

Clinical case
A 71-year-old man, with an uneventful past medical history, was diagnosed with stage IIIB (T4N2MO), epithelial-growth-factor-receptor (EGFR) wild type, lung adenocarcinoma.

The patient underwent 4 cycles of first line chemotherapy with cisplatin/vinorelbine and then radiotherapy, obtaining a partial response.

After 4 months, tumor progression was identified, as assessed by whole-body 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) scan, showing pleural and nodal metastasis. Nivolumab, 3 mg/kg every 2 weeks, was started at this point.

While pre-nivolumab thyroid function was normal, 3 months after starting the therapy, a low serum TSH level of 0.04 mU/L (0.38-5.33) was found, associated with a normal level of FT4, of 10.8 pmol/L (7.9-14.4). Thyroid antibody (Ab) tests, including TSH-receptor Ab, were negative.

At ultrasound examination, thyroid gland parenchyma was normo-echoic, demonstrating an isoechoic thyroid nodule in the right lobe, with regular margins, measuring 14mm diameter. Previous medical history was negative for thyroid disease.

One week after the referred thyroid function tests, nivolumab was discontinued due to progressive disease as assessed by abdominal magnetic resonance, demonstrating right adrenal metastasis and patient started cisplatin/vinorelbine chemotherapy. One month after nivolumab suspension, patient had already normalized thyroid tests, with TSH 2.27 mU/L and FT4 9.1 pmol/L. More recently (6 months after nivolumab discontinuation), thyroid function tests remained stable, with TSH 1.05 mU/mL and T4L 9.4 nmol/L. At this point, patient was receiving permitrexed chemotherapy.

Conclusions
Immune checkpoint molecules as nivolumab, play a crucial role in anti-tumor immunity evasion. Besides its benefits, it may cause irAEs, including TD. We believe it’s essential to perform thyroid function tests at baseline and before the administration of each nivolumab dose, if possible. Additionally, large prospective studies are required in order to assess, the impact of autoimmunity on the development of TD induced by nivolumab, and its potential effect on overall survival and specific cancer survival data.

Thyroid
THYROID DISORDERS CASE REPORTS I

Methimazole-Induced Neutropenia in Premature Twins with Graves’ Disease
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Neuroendocrinology and Pituitary
NEUROENDOCRINOLOGY AND PITUITARY

The Prevalence of Impulse Control Disorders in Patients with Acromegaly and Prolactinomas Treated with Dopamine Agonists
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