A 44-year-old woman with ER+/Her2(-)/PI3K positive metastatic breast cancer was started on alpelisib. Previously, HbA1C was 5.4%. Hyperglycemia developed and HbA1c rose to 9.0% within 6 months of alpelisib 300mg daily. She started metformin and empagliflozin, which she was unable to tolerate due to nausea and vomiting. Her self-monitored blood glucose was 300-400mg/dL within hours after her morning alpelisib dose. We discontinued empagliflozin when she developed metabolic acidosis with an increased anion gap. However, prior to any dose reduction, oncology discontinued alpelisib due to evidence of cancer progression. A week later, her glucose normalized.

Second case is of a 64-year-old woman with stage IV ER+/Her2(-)/PI3K mutated breast cancer with bony metastases, who was started on alpelisib 250mg. Her prior HbA1C was 5.5%. Ten days after initiation of alpelisib, she developed grade 3 hyperglycemia (blood glucose levels 200-500mg/dL). She was started on metformin 2000mg with alpelisib dosed at noon. However, she noted a marked rise in blood glucose in the afternoon, few hours following alpelisib dose. Thus, moving the alpelisib to bedtime allowed better control of glycaemia by using overnight basal insulin.

Similarly, a 37-year-old woman with a history of ER+/HER2(-) stage IV metastatic breast cancer to the liver, with PI3K mutation was found to have acute, severe hyperglycemia with blood glucose of 300mg/dL, despite HbA1C being only 4.7%. This was attributed to initiation of alpelisib 2 days prior to admission. Given the severity of her insulin resistance (requiring > 100 units of insulin daily), alpelisib dose was reduced from 300mg to 150mg/day. On discharge, she was placed on metformin, dulaglutide, and basal and prandial insulins. Her HbA1C rose to 9.4% within 3 months of alpelisib initiation.

This case series demonstrate the unique challenges in managing alpelisib induced reversible hyperglycemia.

Diabetes Mellitus and Glucose Metabolism

**DIABETES CASE REPORTS**

**An Atypical Case of Latent Autoimmune Diabetes of Adults**

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**Introduction**: Latent autoimmune diabetes of adults (LADA) is an adult-onset, slowly progressing subtype of autoimmune type 1 diabetes mellitus (T1DM), that is often misdiagnosed as T2DM. We present an atypical case of LADA that was presented in an uncommonly late age with high titres of anti-glutamic acid decarboxylase antibodies (GADA). **Clinical Case**: A 78 year old male presented with alcohol intoxication and hyperglycemia. His serum glucose was 441mg/dL with negative urine ketones. Arterial blood gas showed pH 7.36, HCO3-20mmol/L, pCO2 37.1mmHg. Anion gap was 11. HbA1c level was 16%. His body weight was 43.2kg with a BMI of 16.6. He was having polyuria and polydipsia, and was recently diagnosed with T2DM. His low BMI and symptoms raised suspicion for LADA. GADA titres revealed to be greater than 250IU/mL. A diagnosis of LADA was made.

He was discharged on insulin. **Conclusion**: LADA shares the same genetic and autoimmune profiles with T1DM, but its insidious presentation overlaps with that of T2DM, often delaying diagnosis and adequate treatment. Our case of confirmed LADA at a late age of 78 is atypical, but warrants that adults newly diagnosed with diabetes should be screened for LADA if there are atypical findings. Among the anti-islet antibodies, GADAs are the most sensitive self antigen-antibody markers of autoimmune diabetes. The GADA titre is often used to stratify the risk of progression to insulin dependence in LADA, as a higher titre suggests severe β-cell loss in the pancreas. High GADA titres at the time of diagnosis in an elderly age is also an uncommon finding for LADA. Autoimmune diseases with aggressive autoimmune responses present early, while indolent progressions lead to late onset of symptoms and diagnosis. Thus it is unusual for our patient to have significantly high GADA levels. As pathophysiology of LADA is yet to be understood, further research may reveal the autoimmune process of GADA and the role of titres in disease activity and progression. There are no current therapeutic guidelines for LADA. Our patient was eventually discharged on insulin given his high HbA1c with high titres of GADA, but there were questions regarding the use of oral glycemic control agents due to his history of noncompliance. The use of oral agents for LADA remains an area of ongoing research. The general understanding is that due to its autoimmune etiology, insulin is eventually required. Early insulin therapy preserves residual β-cell function, improves glycemic control, and reduces the risk of long-term complications. As treatment goals of LADA would be to improve glycemic control with preserving residual β-cell function, further research may establish treatment guidelines for LADA. Monitoring anti-islet antibodies and c-peptide titres may play a role in establishing the timing to introduce oral agents and/or insulin for optimal treatment of LADA.

**Diabetes Mellitus and Glucose Metabolism**

**DIABETES CASE REPORTS**

**An Atypical Presentation of Hyperosmolar Hyperglycemic State Induced by SARS CoV 2**

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Hyperglycemic emergencies such as Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycemic State (HHS) are commonly precipitated by infectious processes. Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) is a novel infectious process prompting hyperglycemic crisis. SARS-CoV-2 at the level of the lungs affects ACE2 functioning which in turns decrease the B cells proliferation at the pancreas and hinders insulin secretion. Advanced age and comorbidities such as hypertension, cardiovascular disease and diabetes mellitus are considered to
be a risk factors for severe illness and mortality between patients with SARS-CoV-2.

We present the case of a 39-year-old woman with medical history of uterine fibroma, who presented with complaints of general malaise, polyuria and polydipsia of one week evolution, associated with sore throat, subjective fever, dry cough, abdominal pain, nausea and vomiting. Physical examination remarkable for dry oral mucosa, decreased skin turgor, and prolonged capillary refill. Vital signs significant for hypertension, tachycardia, and tachypnea. Laboratory work up remarkable for glucose of 1312 mg/dL, HCO3- of 16 mEq/L, serum osmolality of 333 mOsm/kg, serum ketones positive and HbA1C of 15%. ABG’s showed pH of 7.33, PCO2 of 29.8 and a PAO2 of 158.5 mmHg for a high anion gap metabolic acidosis (AG of 15.3 mEq/L), non-anion gap metabolic acidosis with respiratory alkalosis. Chest X-ray revealed bilateral perihilar, peribronchial cuffing. SARS-CoV-2 PCR testing was positive. Clinical and laboratory workup met criteria for diagnosis of HHS and Diabetes Mellitus de Novo most likely secondary to SARS-CoV-2 infection. Patient was treated with aggressive IV hydration and insulin infusion with resolution of hyperglycemia, ketonemia and symptoms.

SARS-CoV-2 infection can precipitate acute metabolic complications in patients with diabetes or unknown diagnosis of diabetes. The effect of the virus could be direct effect on β-cell function. To our knowledge, there are only a few cases reported of HHS precipitated by SARS-CoV-2 infection therefore medical awareness is important for early diagnosis of possible triggering factors such as COVID-19 and early management of patients presenting with new onset hyperglycemic emergencies.

Diabetes Mellitus and Glucose Metabolism

DIABETES CASE REPORTS

An Unusual Case of Latent Autoimmune Diabetes in Adult and Pancreatic Neuroendocrine Tumor in a Patient Presenting With Diabetes

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Introduction: Latent autoimmune diabetes in adults (LADA) and pancreatic neuroendocrine tumors (PNETs) are rare causes of adult-onset diabetes mellitus (DM). The existence of both LADA and a PNET in a single patient has not been previously reported.

Clinical Case: A 65-year-old female with history of type 2 DM diagnosed 15 months ago, on metformin 500mg twice a day presented with fatigue, dry mouth, polyuria, and blury vision for one week and weight loss of 12 pounds over 3 months. Plasma glucose was 599 (nl 65–144 mg/dL) with an elevated anion gap (17; nl 5–15 mmol/L), low bicarbonate (19; nl 21–32 mmol/L) and elevated beta hydroxybutyrate (4.79; nl 0.02–0.27 mmol/L). Diabetic ketoacidosis was diagnosed, and intravenous fluids and insulin were administered. Work up revealed HbA1C of 14% (nl 4.2%-5.6%) which had increased from 7% noted three months ago. Glutamic acid decarboxylase antibodies (GAD65 Ab) was >250 (0.0–0.5 IU/mL) and C peptide was 0.42 (0.81–3.85 ng/mL). A computed tomogram of the abdomen performed to evaluate the acute worsening of her HbA1C revealed a 1.4 x 1.3 cm poorly defined hypoenhancing pancreatic head lesion, which on magnetic resonance imaging was 1.6 x 1.2 cm. Further evaluation showed normal levels of glucagon (127; nl <=208 ng/L), somatostatin (26; nl <=30pg/mL) and vasoactive intestinal peptide (<13; nl 0–60 pg/mL), and an elevated chromogranin A (155; nl 0-95ng/mL). An endoscopic ultrasound guided fine needle aspiration of pancreatic head mass revealed a well differentiated NET with Ki-67 proliferation index of <1%. She underwent pylorus preserving pancreatoduodenectomy and histopathology showed a 2 cm grade one NET on pancreatic head with no involvement of the 23 tested lymph nodes. Immunohistochemistry was positive for chromogranin and synaptophysin and negative for insulin, somatostatin and gastrin, confirming diagnosis of well-differentiated pancreatic NET Stage Ib (T2N0M0). Whole body PET CT scan done 2 months following surgery did not reveal any focal radiotracer uptake to suggest metastasis. Given the presence of GAD65 Ab, age of onset of DM, and an initial non-requirement of insulin, the patient was diagnosed with LADA and insulin therapy was initiated.

Conclusion: We report a unique case of a patient with LADA who was incidentally found to have a non-functioning pancreatic NET. Although functional PNETs such as glucagonoma and somatostatinoma cause hyperglycemia, DM associated with non-functioning NETs is rare, but has been reported with gastrointestinal NETs (1). Our patient likely developed uncontrolled hyperglycemia from LADA but was incidentally found to have a PNET which may have contributed to the worsening of hyperglycemia. This highlights the importance of thorough evaluation for the causes for acute worsening of hyperglycemia.