Sometimes it is a Zebra: Laboratory Diagnostics for Atypical Diabetes Presentations

Stephanie Neary, MPA, MMS, PA-C

Disclosure

- Nothing to disclose

Diagnostics 101

	A1C	FPG	OGTT	Random Plasma Glucose
Normal	Less than 5.7%	Less than 100 mg/dl	Less than 140 mg/dl	-
Prediabetes	5.7% to 6.4%	100 mg/dl to 125 mg/dl	140mg/dl to 199 mg/dl	-
Diabetes	6.5% or higher	126 mg/dl or higher	200 mg/dl or higher	200 mg/dl or higher

A1C (hemoglobin a1c, glycated hemoglobin): hemoglobin linked to sugar
FPG (fasting plasma glucose): glucose level after no food or drink for 8 hours
OGTT (oral glucose tolerance test): blood sugar before and after glucose load

Case 1:

- Ms. A is a 37-year-old female who presented to the ED with a blood glucose of 39. She reports that 6 weeks ago, she was diagnosed with type 2 diabetes (A1C 7.5%) while hospitalized for her third round of chemotherapy for stage IV endometrial cancer. She reports no prior history of prediabetes/diabetes.
- Upon discharge, she followed up with her PCP and was prescribed Metformin 1000mg BID and Lantus 15 units BID and told to check her sugar TID and follow up in 3 months for repeat A1C testing.

What was missed by both the ED and the PCP?

Case 1 continued:

- 9 days before presenting to the ED, Ms. A received her 4th round of chemotherapy, which included high-dose dexamethasone on each of two days preceding treatment and the two days following treatment.
- On the day she presented to the ED, Ms. A reports her blood sugars spiked to 625, for which she gave herself 50 units of Lantus and arrived at the ED later that day with a glucose of 39.

What happened here?

Testing Limitations

	Limitations
A1C	• Lower sensitivity than glucose testing. • Unreliable in patients with certain comorbidities.
FPG	• Limited to current glucose levels that are highly sensitive to changes due to recent carbohydrate intake, stress, or illness. • Less correlation to long-term complications of diabetes than A1C. • Many labs wrongfully test serum glucose.
OGTT	• Impacted by acute changes in stress, illness or medications, caffeine consumption or tobacco use.

	A1C results could be:	Why A1C is impacted:
Sickle cell anemia	Falsely low	Presence of HbF causes assay artifact
Dialysis	Falsely low	Shortened life span of red blood cell (RBC)
Hemolytic anemia	Falsely low	Shortened life span of red blood cell
Chronic liver disease	Falsely low	Bleeding and hemolysis shorten RBC lifespan
Erythropoietin treatment	Falsely low	New RBCs in circulation
Blood transfusions	Falsely low	New RBCs in circulation
Antiretroviral treatment for HIV	Falsely low	Causes low hemolytic state that shortens RBC lifespan
Thalassemia	Falsely low	HB S-beta causes shortened RBC lifespan
Iron deficiency anemia	Falsely high	Increased RBC lifespan
Steroid use	Falsely high	Steroid-induced hyperglycemia

IF IT CHANGES THE RBC LIFESPAN, IT WILL CHANGE A1C RELIABILITY!

Case 1 continued:

- Through further discussion, it is discovered that while she reports very high blood sugars for the two weeks following her chemotherapy, she reports 'normal' sugars for the remainder of the time between treatments.

How can we adjust her regimen?

Metformin 1000 BID, Lantus 15 BID

- Ms. A was discharged on two separate insulin regimens
  - Two weeks following chemotherapy:
    - Lantus 30 units QHS, Regular 3ac and Regular 3:50>150ac>200hs
  - Remaining days until next round of chemotherapy begins:
    - Lantus 20 units QHS, Regular 3ac and Regular 1:50>150ac>200hs

Case 2:

- Ms. C is a 40 yo female diagnosed with gestational diabetes 10 years ago during her 1st pregnancy and diagnosed with T2DM 3 years ago. She was referred to Endocrinology with a sudden increase in her A1C to 10.1%.

  - Recent A1C:
    - December 2018: 6.4%
    - March 2019: 7.1%
    - June 2019: 6.9%
    - **September 2019: 10.1%**

Case 2 Continued:

- Pt exercises (running and weights) at least 4-5 times a week for at least 45 min - 1 hr.
- Diet is very low carbohydrate, high protein, and overall low fat consisting of small, frequent meals.
- Denies polydipsia, polyphagia, polyuria, n/v, abdominal pain, blurred vision

- PE: unremarkable
- Vitals*:*
  - BP 116/77
  - Pulse 58
  - Temp 36.7 °C (98 °F)
  - Ht 167.6 cm (5' 5.98")
  - Wt 67.4 kg (148 lb 9.6 oz)
  - BMI 24.00 kg/m²

Still no explanation for the A1C increase

Case 2 Continued:

- Current medications:
  - Fortamet (metformin hcl) 500 mg PO BID
  - Victoza (liraglutide) 1.2mg daily
  - *Patient denies any medication side effects*
- Non-obese, active, healthy diet, no medication changes, previously well controlled…

What labs should we consider?

Case 2 Continued:

- GAD antibodies: 156 IU/mL — **ELEVATED**
- Anti-islet cell antibodies: <1:4 — Not elevated
- C-peptide: 1.42 ng/mL — Not stimulated- VOID
  - Glucose 89

Type 1 Diabetes

- Immune-mediated type 1 diabetes will have at least one type of autoantibody present:
  - Islet cell autoantibodies
  - Autoantibodies to insulin
  - Autoantibodies to GAD (GAD65)
  - Autoantibodies to the tyrosine phosphatases 1A-2 and IA-2B
  - Autoantibodies to zinc transporter 8 (ZnT8)
- C-peptide will be reduced
  - A measure of endogenous insulin production
  - Preproinsulin -> proinsulin -> c-peptide + insulin

MUST ORDER SERUM GLUCOSE AT THE SAME TIME!

What is her diagnosis?

- Patients who are above age 30 at the onset of diabetes, with normal BMI, appear to be resistant to oral medications, and/or have a sudden change in A1C ….. **consider LADA**

- LADA (latent autoimmune diabetes in adults)
  - Slowly progressing, autoimmune
  - High presentation variability; features of both type 1 and type 2
  - Accounts for 2-12% of all patients with adult-onset diabetes

Case 2 Continued:

- *Old regimen: Metformin 500 mg PO BID, Victoza 1.2mg daily*
- New plan:
  - Metformin XR 1000 mg po BID
  - Start small dose basal insulin. (0.2units/kg = 13 units, 0.1unit/kg=6.7) Started at 6 units QAM
  - Check sugars ACHS and send numbers to clinic in 1 week. Call if sugars <70 or >350

- C-peptide level :
  - <0.3 nmol/L
    - insulin
  - ≥ 0.3 nmol/L - ≤0.7 nmol/L
    - Metformin +/- SGLT-2 or insulin
    - Comorbidities drive tx
  - ≥ 0.7 nmol/L
    - Follow ADA T2DM guidelines

Repeat c-peptide every 6 months

Additional Diagnostic Considerations

- What if GAD antibodies were not positive?
  - Consider pancreatitis, monogenic diabetes
- Monogenic Diabetes
  - Maturity onset diabetes of the young (MODY)
    - Inherited, autosomal dominant (multiple genetic mutations identified)
    - Typical presentation: subacute ketosis, non-obese, lack of comorbidities seen with T2DM
    - **Diagnostics: c-peptide remains normal, GAD antibodies are negative; genetic testing**
  - Neonatal diabetes mellitus (NDM)
    - Genetic, onset typically <12 months of life
    - May be permanent (PNDM) or transient (TNDM)
    - **Diagnostics: genetic testing**

Additional Diagnostic Considerations

- In the presence of hemoglobinopathies?
  - **Fructosamine or glycated albumin (GA)**
  - Predictive of blood sugar over the past 2-3 weeks
  - Great for sickle-cell anemia, post-transplant or medication change monitoring (not for every patient!)
  - **NOT DIAGNOSTIC** because no standardization exists
  - Any condition that impacts serum albumin will cause **both** tests to be unreliable

Hyperglycemia-Associated Conditions

- Hereditary hemochromatosis:
  - “bronze diabetes”
  - **Diagnosis**: Genetic testing (iron panel, LFTs)
- Pancreatic cancer:
  - Risk for DM vs DM as risk factor? Consider in “atypical” new-onset
  - **Diagnosis**: CT scan, biopsy
- Cushing’s syndrome:
  - Chronic hypercortisolism -> insulin resistance and decreased production
  - **Diagnosis**: ADA diagnostic criteria for T2DM

Hyperglycemia-Associated Conditions

- Cystic fibrosis:
  - Cystic fibrosis related diabetes (CFDM)
  - ~50% of adults with CF
  - **Diagnosis**: OGTT; recommended annual screening starting at age 10
- Polycystic Ovarian Syndrome (PCOS):
  - Insulin resistance seen in 50-80% of women
  - **Diagnosis**: OGTT screening at PCOS diagnosis

Immunotherapy

- Evidence of spontaneous onset of type 1 diabetes mellitus after use of programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) inhibitor
  - T cell activation by PD1 blockade → beta cell destruction
- Patients may present with beta-cell antibodies, in DKA and/or with low c-peptide → INSULIN DEPENDENCE

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Take Home Points

- If it changes the RBC lifespan, it will change the A1C
- Sudden increase in A1C/insulin requirements → think LADA
  - Test antibodies and c-peptide (and serum glucose)
- Many chronic conditions can cause hyperglycemia

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