66 yo F with Hyperglycemia

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Endorama
June 30, 2016
CC: 66 F who presents with hyperglycemia

- HPI: Hx of metastatic NSCLC referred from for management of new onset diabetes.

- Meals:
  - B: Breakfast bar, Jell-O, Applesauce, Dry cereal
  - L: Bagel, coffee
  - D: Spaghetti, corn, chicken
  - Dessert: avoiding; No sugar-sweetened beverages

- Home BG Monitoring:
  - Fasting sugars 161-274
  - Post-prandial: up to 364

- Metformin → nausea, diarrhea
  - Low carb diet – limited by nausea
CC: 66 F who presents with hyperglycemia

- ROS: notable for fatigue and hyperglycemia otherwise unremarkable
- PMH: Lung Adenocarcinoma, osteoporosis
- PSH: RUL, LUL lobectomy, tonsillectomy, breast lumpectomy
- Soc: Former smoker 15 py (quit 2000); EtOH: 1-2 shots whiskey per day
- FH: Mother with DM2 (dx late, not on insulin until her 90s)
- Current meds: ibandronate 150 mg monthly, rociletinib (EGFR inhibitor - CO-1686), prochlorperazine
Physical Exam – generally unremarkable

- VS: T 98.6F, BP 153/88, P 71, RR 16, SpO2 97% RA, Ht 167.6 cm, Wt 145 lb, BMI 23.4 kg/m²

- Constitutional: She is oriented to person, place, and time. She appears well-developed and well-nourished.
- Head: Normocephalic and atraumatic.
- Eyes: Conjunctivae are normal. Pupils are equal, round, and reactive to light.
- Cardiovascular: Normal rate and regular rhythm.
- Pulmonary/Chest: Effort normal and breath sounds normal.
- Abdominal: Soft. Bowel sounds are normal. Musculoskeletal: She exhibits no edema.
- Neurological: She is alert and oriented to person, place, and time.
- Skin: Skin is warm and dry.
- Psychiatric: She has a normal mood and affect. Her behavior is normal. Judgment and thought content normal.
Labs from initial Endocrine visit:

7/17/15

146 107 12

Ca 9.6
Mg 2.1
Ph 3.2

254

6.5 4.3
0.5 6
12 50

HbA1c: 9.3%
C-peptide: 2.08

What would you like to do?
Approach to glycemic treatment T2DM – A1c 9-10%
Our Plan:

- Start sitagliptin 50 mg daily, uptitrate to 100 mg daily
- Add canagliflozin if not at target
- Insulin as third line
- Avoid pioglitazone given hx of osteoporosis and increased risk of fracture
- Monitor blood sugars fasting and HS and touch base in a week
Additional history:

- October 2011: presented with respiratory infection and incidentally noted RUL mass on imaging, differentiated adenocarcinoma.
- RUL Lobectomy, cisplatin/pemetrexed.
- March 2013 PD: LUL lobectomy
  - Sequencing of mass: EGFR exon 19 deletion, started on erlotinib (1st gen EGFR TKI)
- July 2014 PD: afatinib (2nd gen EGFR TKI)
- March 2015 PD: RLL biopsy with Foundation One testing revealed EGFR T790M mutation and enrolled in a clinical trial with rociletinib (3rd gen EGFR TKI)
EGFR in lung cancer

- EGFR mutations present in 17% of lung cancer
  - 10% Caucasian, 50% Asian patients (more common in non-smokers)
  - Mutation in the Kinase domain → constitutive activation which prevents normal apoptosis of cancer cells
  - 78% response rate to EGFR TKIs (erlotinib, gefitinib)
    - Compared to platinum-based chemotherapy, targeted EGFR inhibitors:
      - Better PFS
      - No change in OS
    - Acquired resistance due to EGFR T790M mutation in 60-70% of patients following initial therapy

Morgensztern et al. JAMA Oncol. 2015;1(2):146-148
Lee et al. JNCI. Vol. 105, Issue 9 | May 1, 2013
Rociletinib is a 3rd generation TKI that specifically targets T790M

- T790M mutation
  - More common in patients with acquired resistance following prior EGFR inhibitor treatment
  - Located in the kinase domain of the protein

Rociletinib is active in EGFR T790M NSCLC

- Phase 1-2 dose finding study
  - Phase 1
    - Primary objectives: Safety, Side effect profile, Pharmacokinetics
    - Secondary objective: Response rate, duration of response, progression-free survival, QOL
  - Phase 2
    - Primary endpoints: Response rate, duration
    - Secondary endpoints: as above

- 130 patients with NSCLC
  - Previously treated with EGFR TKI
  - Median # of prior treatments tried: 4
  - 50% with metastatic disease (44% to brain)

- 78/172 patients screened for phase 2 → T790M positive.
  - Treated in 21 day cycles until PD, toxicity or withdrawal of consent
  - No maximum tolerated dose - **only dose limiting A.E. was hyperglycemia**

Rociletinib is active in EGFR T790M NSCLC

Rociletinib is active in EGFR T790M NSCLC


- **Response rate**
  - **T790M Positive patients:** 59%
  - **T790M Negative patients:** 29%
Rociletinib: Hyperglycemia is the most common A.E.

**Table 4. Treatment-Related Adverse Events in the 92 Patients Receiving Therapeutic Doses of Rociletinib, According to Event Grade.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia†</td>
<td>43 (47)</td>
<td>14 (15)</td>
<td>9 (10)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (35)</td>
<td>16 (17)</td>
<td>14 (15)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (24)</td>
<td>9 (10)</td>
<td>9 (10)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (22)</td>
<td>16 (17)</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18 (20)</td>
<td>10 (11)</td>
<td>7 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (14)</td>
<td>9 (10)</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>11 (12)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>10 (11)</td>
<td>9 (10)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* Shown are events with a number or percentage equal to or greater than 10%.
† Therapeutic dose was 750 mg twice daily, and 1000 mg twice daily of the hydrogen bromide salt form.
‡ Hyperglycemia includes the combined terms of increased blood glucose level, glucose intolerance, impaired glucose tolerance, and hyperglycemia.
Returning to our patient: **Rewind** to review pre-treatment labs and initial monitoring.
Initial management strategy by oncology:

- Rociletinib held – also having transaminitis; confounded by EtOH and Tylenol use
- Resolution of Hyperglycemia
- Started on metformin but having issues with nausea and diarrhea
- Referral to Endocrinology
Our Plan:

- Start sitagliptin 50 mg daily, uptitrate to 100 mg daily
- Add canagliflozin if not at target
- Insulin as third line
- Avoid pioglitazone given hx of osteoporosis and increased risk of fracture
- Monitor blood sugars fasting and HS and touch base in a week.
- Low carb diet
Endo visit: 1 week follow up labs

8/5/2015

<table>
<thead>
<tr>
<th>139</th>
<th>98</th>
<th>26</th>
<th>326</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>15</td>
<td>1.2</td>
<td>326</td>
</tr>
</tbody>
</table>

Ca 10.6
Mg 2.1
Ph 4.0

6.7 4.2
0.9 14
103 230

β-hydroxybutyrate: 6.94

- What would you like to do now?
- Insulin start
- Home ketone monitoring
### Home ketone monitoring

<table>
<thead>
<tr>
<th>Urine Ketones</th>
<th>Blood Ketones</th>
<th>Give this much extra fast acting insulin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>under 0.6</td>
<td>No extra insulin; give correction every 3 hours.</td>
</tr>
<tr>
<td>Small</td>
<td>0.6 - 1.5</td>
<td>Increase correction by 5% and recheck BG in 3 hours.</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.5 - 3</td>
<td>Increase correction by 10% and consult with the advice nurse or the MD on call and recheck BG in 3 hours.</td>
</tr>
<tr>
<td>Large</td>
<td>over 3</td>
<td>Increase correction by 20% and consult with the advice nurse or the MD on call. Check BG in 3 hours.</td>
</tr>
</tbody>
</table>

- **Fluids to prevent dehydration**
  - If blood sugars > 200 mg/dl, drink sugar-free fluids.
  - If blood sugars < 200 mg/dl, drink small amounts of sweetened fluids (sports drinks, Pedialyte, diluted juice)

[https://diabetes.ucsf.edu/sites/diabetes.ucsf.edu/files/Sick%20Day%20Final%2011%2023%2009_0.pdf](https://diabetes.ucsf.edu/sites/diabetes.ucsf.edu/files/Sick%20Day%20Final%2011%2023%2009_0.pdf)
Repeat labs look better

8/12/2015

<table>
<thead>
<tr>
<th></th>
<th>142</th>
<th>106</th>
<th>20</th>
<th>113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>9.6</td>
<td></td>
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<td>Ph</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

β-hydroxybutyrate: <0.10
Blood sugars stably improved on insulin
Continued course...
Continued course...

On  Off drug

Glucose (mg/dL)

Insulin (U)
No insulin required when off drug

On  Off drug
Insulin Insufficiency vs. Resistance?

- Transient and reversible beta-cell dysfunction with DKA
- Suggests primary defect is insulin insufficiency rather than resistance
- Normalization of blood sugars with minimal amounts of insulin (0.3-0.5 U/kg/d)
Back to our patient: Insulin secretion appears to be intact.
Utility of C-peptide in predicting insulin secretion

Diabetes subtype:
- Type 1
- Type 2

C-peptide test:
- Non-fasting ‘random’
- Fasting
- Glucagon stimulated

Glucose >144 mg/dL

Suggested C-peptide thresholds to guide clinical practice

<table>
<thead>
<tr>
<th>Clinical role</th>
<th>Stimulated (non-fasting ‘random’/post-glucagon/mixed-meal test) (nmol/l)</th>
<th>Fasting (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute insulin deficiency/absolute insulin requirement [76]</td>
<td>&lt; 0.2</td>
<td>&lt; 0.08</td>
</tr>
<tr>
<td>Likely Type 1 diabetes/inability to achieve glycaemic control with non-insulin therapies [39,40,95]</td>
<td>&lt; 0.6</td>
<td>&lt; 0.25</td>
</tr>
<tr>
<td>Suggests Type 2 or monogenic (MODY) diabetes in a patient with presumed Type 1 diabetes &gt; 3–5 years post-diagnosis [65,71]</td>
<td>&gt; 0.2</td>
<td>&gt; 0.08</td>
</tr>
<tr>
<td>Consider MODY/Type 2 diabetes in young onset diabetes at diagnosis [67]</td>
<td>&gt; 1</td>
<td>&gt; 0.4</td>
</tr>
</tbody>
</table>

Potential mechanisms for drug-induced hyperglycemia

- **Pancreatic effects**
  - Reduced beta-cell function/mass
  - Impaired insulin secretion - C-peptide levels suggest against this
    - DKA - suggests primary defect is insulin insufficiency rather than resistance
    - Normalization of blood sugars with minimal amounts of insulin (0.3-0.5 U/kg/d)

- **Hepatic effects**
  - Inhibition of glycogen synthesis/Increased gluconeogenesis
  - Increased glycogenolysis

- **Peripheral effects**
  - Reduced peripheral glucose uptake

- NEJM report alludes to preclinical data (rats) suggesting that drug metabolite inhibits IGF-1R and insulin R signaling
  - Increased hepatic gluconeogenesis
  - Reduced peripheral glucose uptake
  - Hyperglycemia-mediated beta cell impairment
**Recommended monitoring**

<table>
<thead>
<tr>
<th><strong>Fasting blood glucose (FBG) monitoring:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Screening/baseline visit; cycle 1: day 1, 8, 15; cycle 2 and beyond: day 1; end of treatment visit</td>
</tr>
</tbody>
</table>

**Initial home monitoring:**

- Daily (alternate between fasting glucose and pre-dinner glucose)

**General treatment goals:**

- Fasting plasma glucose <160 mg/dL; random plasma glucose <200 mg/dL; HbA1c ≤8%
- Lifestyle modifications (refer to nutritionist or diabetes specialist if needed)†

**Pre-existing diabetes:**

- Continue current home glucose monitoring regimen; adjust frequency of monitoring and/or diabetic medication according to standard guidelines and grade of hyperglycemia

**Provider should be contacted for:**

- FBG >160 mg/dL
- Presence of hyperglycemia symptoms (polydipsia, polyuria, polyphagia, blurry vision)

**NOTE:** Hyperglycemia generally occurs within the first 3 weeks of treatment
Recommended treatment

- Hold drug until resolution (FBG <250)
- Increased home monitoring
- Second oral agent/insulin
- Fluids if signs/symptoms of dehydration

**Grade 2 hyperglycemia**
(FBG >160 to 250 mg/dL; >8.9 to 13.9 mmol/L)
- EGFR TKI targeting T790M may continue without interruption or dose reduction in asymptomatic patients
- Hold EGFR TKI targeting T790M for 48 to 72 hours if symptomatic
- Twice daily home monitoring (before breakfast and dinner)

**Asymptomatic**
- Repeat FBG within 1 week—if grade 2 results at least twice in 1 week, start antihyperglycemic agent (metformin 500 mg orally twice daily)
- Continue home monitoring—if worsens or no improvement, treat according to grade 3 or 4

**Symptomatic**
- Start antihyperglycemic agent (metformin 500 mg orally twice daily)
- Continue home monitoring—if worsens or no improvement, treat according to grade 3 or 4
References

- Standards of Medical Care in Diabetes 2016. Diabetes Care Volume 39, Supplement 1
- Morgensztern et al. JAMA Oncol. 2015;1(2):146-148
- Lee et al. JNCI. Vol. 105, Issue 9 | May 1, 2013
- https://diabetes.ucsf.edu/sites/diabetes.ucsf.edu/files/Sick%20Day%20Final%2011%2023%2009_0.pdf
- Villadolid et al. Translational Lung Cancer Research 4, 576–583