28 M with ALL presenting with pancreatitis

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Endorama June 1, 2017
HPI

28 M with B-ALL with CNS involvement who presented with abdominal pain. He presented to clinic with abdominal pain 5/10 and several episodes of diarrhea. He was febrile in clinic to 38.5 with tachycardia to 120s.

He was given tylenol, IV fluids, dilaudid, ceftriaxone empirically, and admitted from clinic.

Labs showed elevated lipase of 510 and TG > 4425.

Endocrinology consulted for further management.
Extended History

**PMH:** B-ALL, denies that his cholesterol had ever been checked before

- Diagnosed 4 months prior when he presented with fatigue and back pain
- Found to be pancytopenic (Hgb 6.1, WBC 3.2, Plt 61) with multiple enhancing foci within multiple vertebral bodies
- Found to have CNS involvement
- Started on CALGB chemotherapy that includes cyclophosphamide, cytarabine, intrathecal and IV methotrexate, pegasparargase, vincristine
Extended History

**Home medications:** Acetaminopen-caffeine butalbital, Acyclovir, Famotidine, lorazepam PRN for nausea/vomiting, scopolamine patch, ondansetron, polyethylene glycol, sennosides-docusate, bactrim, ursodial

**PSH:** None

**Allergies:** NKDA

**Social history:** Coast guard mechanic, previously used to drink 6-12 beers per week but has stopped since diagnosis. Non-smoker. Married with a 3 year old child.

**Family history:** No one with early CVD or high cholesterol. DM in mother.
Exam

T 37.6, P 126, BP 121/71, R 23, SpO2 94%, Ht 5’11, Wt 76.8 kg, BMI 23.4
Gen: No acute distress
HEENT: EOMI, oropharynx clear
Neck: supple, no thyromegaly
Lung: Normal respiratory effort, course breath sounds
Chest wall: no tenderness or deformity
CV: tachycardic, regular, no murmurs
Abdomen: Soft, diffusely tender, bowel sounds present
Extremities: Normal, atraumatic
Skin: No xanthomas
Neuro: Alert, cooperative
Psych: Normal mood and affect
Initial Labs

- Amylase 145
- Lipase 510
- TG > 4425

Ca 9.2
Mg 1.9
P 2.9

6.2 3.5
1.2
53 85
80

15.2
35
179

Couldn’t run due to lipemia
Recommendations overnight?

- Conservative measures
  - (IV fluids, NPO, pain control)
- Recheck lipase and TG to trend
Asparaginase

- Derived from E. coli
- Depletes external sources of asparagine
  - Most malignant lymphocytes have limited asparagine synthetase activity
  - Lack of asparagine leads to apoptosis
- Known toxicities: Hypersensitivity, pancreatitis, severe hyperlipidemia, altered liver function, allergic reactions, thrombosis
Asparaginase induced pancreatitis

- Unknown mechanism and usually not associated with hyperTG
- Usually occurs relatively early in the course of therapy, suggesting it is related to a genetic predisposition rather than cumulative dose
  - Our patient had received 3 doses
  - Recent GWAS study identified variants in a pancreatic carboxypeptidase seemed to predispose individuals to pancreatitis but the mechanism is not clear
- Greater risk with older age with adults having 5% risk

Asparaginase-induced Hypertriglyceridemia

- Related to increases in endogeneous synthesis of vLDL and decreased lipoprotein lipase activity

→ leads to decreased removal of TG from plasma
B-48, B-100, C-II, C-III, E indicate apolipoproteins B-48, B-100, C-II, C-III, and E

LPL = lipoprotein lipase
FFAs = free fatty acids
CMR = chylomicron remnant
Apo-A-V = apolipoprotein A-V
LDL = low density lipoprotein

LRP = LDL receptor-related protein
LDL-R = LDL receptor
VLDL = very low density lipoprotein
VLDL-R = VLDL remnant
IDL = intermediate density lipoprotein

Next set of labs

- Amylase 145 → 205
- Lipase 510 → 1155
- TG > 4425 → >4425 (No change)
- Lactic Acid 5.0

Couldn't run due to lipemia
Now what?
Hypertriglyceridemia-induced pancreatitis

- There is a paucity of data or guidance
- No large studies of plasmapheresis or insulin
- No studies comparing plasmapheresis vs insulin
- Four lines in Endocrine Society guidelines for hyperTG: “We do not recommend the use of heparin infusion or plasmapheresis in the treatment of very severe hypertriglyceridemia with pancreatitis. The treatment of underlying causes including dietary fat restriction and use of long-term fibrate therapy should suffice”
Plasmapheresis

- Quickly removes TG
- Also thought to remove circulating activated enzymes, proteases, and inflammatory mediators
- HyperTG is a Category III indication ("optimum role of apheresis is not established, decision making should be individualized") for plasmapheresis per the American Society of Apheresis
<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Design</th>
<th>TG Drop</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen</td>
<td>20</td>
<td>Retrospective review Compared to 40 patients who did not receive TPE and/or 34 treated before TPE was available</td>
<td>2019± 780 → 691± 333</td>
<td>“No difference in morbidity or mortality” but small &amp; not a RTC. Patients who rec’d TPE seemed to have worse pancreatitis.</td>
</tr>
<tr>
<td>Yeh</td>
<td>18</td>
<td>Retrospective review of patients refractory to previous therapy. No comparator group.</td>
<td>1971± 761 → 693± NR</td>
<td>Effective and well tolerated</td>
</tr>
<tr>
<td>Gubensek</td>
<td>50</td>
<td>Retrospective review. No comparator group.</td>
<td>5212±3610 → 956±956</td>
<td>Two cases of hypotension, one with GI bleeding (heparin) 15% mortality in subset of 40</td>
</tr>
</tbody>
</table>
**Table 1. Clinical characteristics and critical scores of the patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Ranson score</th>
<th>Glasgow pancreatitis score</th>
<th>APACHE II score</th>
<th>CRP level (normal &lt;0.8 mg/dl) mg/dl</th>
<th>Baltazar CT stage score</th>
<th>Type of hyperlipidemia (Frederickson classification)</th>
<th>APACHE II score after plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>6</td>
<td>4</td>
<td>12</td>
<td>14</td>
<td>4</td>
<td>V</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>6</td>
<td>5</td>
<td>16</td>
<td>17</td>
<td>5</td>
<td>V</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>4</td>
<td>3</td>
<td>11</td>
<td>10</td>
<td>4</td>
<td>IV</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>7</td>
<td>5</td>
<td>16</td>
<td>12</td>
<td>10</td>
<td>V</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>6</td>
<td>5</td>
<td>17</td>
<td>17</td>
<td>7</td>
<td>IV</td>
<td>13</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein.

11.3 mmol/L = 1000 mg/dL

**Table 2. Results of the patients treated with plasmapheresis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Triglycerides (normal 0.34–1.7 mmol/l)</th>
<th>Improvement</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>admission before</td>
<td>1st plasmapheresis after</td>
<td>2nd plasmapheresis before</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>17</td>
<td>10.9</td>
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<tr>
<td>3</td>
<td>12</td>
<td>19</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>20</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>13</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Insulin

- Potent activator of lipoprotein lipase
- Also inhibits hormone-sensitive lipase in adipocytes, which breaks down adipocyte TG and releases free fatty acids into the circulation
- Often requires aggressive dosing, e.g. 0.1-0.3 units/kg/hr
  - Will require dextrose containing IV fluids if patient does not have diabetes
- Effective but generally slower
Case series of 12 patients treated with insulin gtt

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Age [years]/gender</td>
<td>41/Male</td>
<td>48/Female</td>
<td>54/Male</td>
<td>35/Male</td>
<td>43/Female</td>
<td>30/Female</td>
<td>59/Male</td>
<td>46/Male</td>
<td>40/Female</td>
<td>45/Male</td>
<td>65/Male</td>
<td>46/Male</td>
<td>46</td>
<td>9.75</td>
</tr>
<tr>
<td>Serum amylase (25–125 U/l)</td>
<td>155</td>
<td>128</td>
<td>84</td>
<td>635</td>
<td>497</td>
<td>259</td>
<td>780</td>
<td>368</td>
<td>424</td>
<td>490</td>
<td>530</td>
<td>330</td>
<td>390.00</td>
<td>211.72</td>
</tr>
<tr>
<td>Serum lipase (10–60 U/l)</td>
<td>350</td>
<td>286</td>
<td>196</td>
<td>376</td>
<td>138</td>
<td>86</td>
<td>420</td>
<td>115</td>
<td>146</td>
<td>198</td>
<td>245</td>
<td>166</td>
<td>226.83</td>
<td>109.05</td>
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<tr>
<td>Serum calcium (9–11 mg/dl)</td>
<td>8.5</td>
<td>8.4</td>
<td>9.6</td>
<td>8.3</td>
<td>6.8</td>
<td>7.4</td>
<td>7.8</td>
<td>9.2</td>
<td>8.4</td>
<td>7.6</td>
<td>8.5</td>
<td>8.8</td>
<td>8.27</td>
<td>0.77</td>
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<tr>
<td>Serum triglycerides (50–250 mg/dl):</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d1</td>
<td>1118</td>
<td>1176</td>
<td>1228</td>
<td>1027</td>
<td>1004</td>
<td>1130</td>
<td>1156</td>
<td>1124</td>
<td>1235</td>
<td>1190</td>
<td>1215</td>
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<td>74.74</td>
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<tr>
<td>d2</td>
<td>540</td>
<td>635</td>
<td>712</td>
<td>760</td>
<td>684</td>
<td>756</td>
<td>710</td>
<td>654</td>
<td>785</td>
<td>796</td>
<td>810</td>
<td>774</td>
<td>718.00</td>
<td>79.37</td>
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<tr>
<td>d3</td>
<td>355</td>
<td>464</td>
<td>489</td>
<td>496</td>
<td>476</td>
<td>481</td>
<td>528</td>
<td>498</td>
<td>494</td>
<td>524</td>
<td>590</td>
<td>520</td>
<td>492.92</td>
<td>54.51</td>
</tr>
<tr>
<td>d4</td>
<td>272</td>
<td>248</td>
<td>385</td>
<td>415</td>
<td>346</td>
<td>390</td>
<td>425</td>
<td>432</td>
<td>384</td>
<td>434</td>
<td>445</td>
<td>370</td>
<td>378.83</td>
<td>62.93</td>
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<tr>
<td>d5</td>
<td>243</td>
<td>232</td>
<td>358</td>
<td>366</td>
<td>252</td>
<td>324</td>
<td>373</td>
<td>290</td>
<td>296</td>
<td>276</td>
<td>356</td>
<td>298</td>
<td>305.33</td>
<td>49.81</td>
</tr>
</tbody>
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LRP = LDL receptor-related protein

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Heparin

- Temporarily increases lipoprotein lipase
- But there is an increase in lipoprotein lipase metabolism by the liver, thus making the effect temporary
- Generally has fallen out of favor
Acute pancreatitis (AP) diagnosed with two of three:
- Abdominal pain compatible with AP
- Serum lipase >3 times upper limit of normal
- Imaging studies consistent with AP
Note: Serum amylase levels may be normal in the presence of hypertriglyceridemia (HTG)

HTG diagnosed when the serum triglyceride level is >1000 mg/dL or the serum is grossly lipemic
Evaluate the patient for primary and secondary causes of HTG

Initiate conventional treatment for AP, including but not restricted to:
- Aggressive hydration
- Analgesia
- Evaluation for and treatment of other potential causes (eg, gallstone pancreatitis)

Does patient have concurrent hyperglycemia?
Yes
Consider intravenous (IV) insulin for glucose and HTG control

No
Is apheresis available?
Can the patient tolerate apheresis?
Yes
Consider apheresis using therapeutic plasma exchange

No
Consider IV insulin with IV glucose supplementation as necessary for HTG control
Initiate an oral triglyceride-lowering medication when the patient can tolerate it

Does patient have severe acute pancreatitis with hypocalcemia, lactic acidosis and lipase >3 ULN (independent of glycemia)

No
Consider apheresis Initiate an oral triglyceride-lowering medication when the patient can tolerate it

Yes
Consider apheresis Initiate an oral triglyceride lowering medication when the patients can tolerate it

Continuously evaluate the patient for and treat complicated disease infection, pancreatic duct injury, extra-pancreatic organ dysfunction)
Clinical Course

- We recommended plasmapheresis x 2
- Start Fenofibrate 145 mg daily when able
- Check lipid panel in the future
- Primary team also started octreotid 100 mcg q8h
Octreotide

- Theoretically is beneficial in pancreatitis to reduce pancreatic enzymes that can cause glandular destruction
- Has been trialed for pancreatitis in general with mild effects seen
- There are specific case reports in asparaginase associated pancreatitis
  - Particularly appealing in children given its relative safety

## TG and Lipase Trend

<table>
<thead>
<tr>
<th></th>
<th>12/6</th>
<th>12/7</th>
<th>12/9 4 AM</th>
<th>12/9 11 AM</th>
<th>12/10</th>
<th>12/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>&gt;4425</td>
<td>5910</td>
<td>659</td>
<td>757</td>
<td>294</td>
<td>402</td>
</tr>
<tr>
<td>Lipase</td>
<td>518</td>
<td>1155</td>
<td>194</td>
<td>68</td>
<td></td>
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</tbody>
</table>

Plasmapheresis

<table>
<thead>
<tr>
<th></th>
<th>12/12</th>
<th>12/14</th>
<th>12/16</th>
<th>12/21</th>
<th>12/23</th>
<th>12/30</th>
</tr>
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<tbody>
<tr>
<td>TG</td>
<td>478</td>
<td>381</td>
<td>308</td>
<td>202</td>
<td>198</td>
<td>138</td>
</tr>
<tr>
<td>Lipase</td>
<td>42</td>
<td>68</td>
<td>83</td>
<td>101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is asparaginase now contraindicated?

- Asparaginase has proven mortality benefit in ALL
- Expert panel on asparaginase toxicities recommends permanently discontinuing asparaginase for clinical pancreatitis with amylase or lipase > 3 x ULN for >3 days
  - OK to continue if no clinical symptoms
  - OK to continue for hyperTG > 1000 if no pancreatitis, once TG returns to the normal range

Follow-up

- Has done well since discharge, only 1 hospitalization for chemo
- Remained on fibrate until recently when repeat TG was found to be 119
- Patient tolerated a modified regimen without asparaginase, currently on maintenance therapy
References


