41 year-old Female with Chronic Pancreatitis Status-Post Total Pancreatectomy and Islet Cell Auto-Transplantation

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University of Chicago
ENDORAMA
Thursday, June 26th, 2014
Chief Complaint

- 41 year-old female with a history of recurrent pancreatitis presented to surgery clinic for surgical treatment of chronic pancreatitis.
History of Present Illness

- 1991 (19 yo): 1\textsuperscript{st} bout of pancreatitis (Arizona)
  - Suspected 2/2 to cholelithiasis
  - ERCP -> noted pancreas divisum
  - 12/1991: first pancreatic duct stent placed
  - 1991-2001: Multiple recurrent episodes of pancreatitis
- 2001 (29 yo): Minor pancreatic duct sphincteroplasty
  - -> 3 years of relief
- 2004-2007: Multiple episodes of recurrent pancreatitis
- 2007: Frey Procedure -> 3 months of relief
- 2008: Evaluated by transplant surgery at UCMC
  - Signs and symptoms consistent with chronic pancreatitis
Genetic Testing for Hereditary Pancreatitis

<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test As Ordered</td>
<td>TEST = PANCREATITIS PANEL TO AMBRY</td>
</tr>
<tr>
<td></td>
<td>RESULT:</td>
</tr>
<tr>
<td></td>
<td>CFTR = KNOWN MUTATION R1162L, NO NOVEL MUTATIONS DETECTED</td>
</tr>
<tr>
<td></td>
<td>CFTR DEL/DUP = NONE DETECTED</td>
</tr>
<tr>
<td></td>
<td>PRSSI, SPINK1 = NO KNOWN OR NOVEL MUTATIONS DETECTED</td>
</tr>
<tr>
<td></td>
<td>PERFORMED BY AMBRY GENETICS, CA 92656</td>
</tr>
</tbody>
</table>
Hereditary Pancreatitis

- Small subset of cases of chronic pancreatitis
- > 30 known mutations described since 1996
  - Most common mutations: $R_{122}H$, $N_{291}$, $A_{16}V$ (PRSS1 gene)
  - Others: $SPINK\ 1$, $CFTR$

- Disease Course:
  - Begin < 10 yo: Epigastric pain, acute pancreatitis
  - Early 20’s: chronic pancreatitis morphologic changes
  - Later: Exocrine insufficiency and Endocrine insufficiency
  - 44% risk of pancreatic cancer by 70 yr after onset sxms

Presents to Surgery Clinic 1/2014

- **Symptoms:**
  - Constant epigastric abdominal pain: rated 6/10
    - -> Morphine 80 mg SR and short-acting PRN
  - Intermittent nausea
  - Anorexia
    - Tolerating Carnation Instant Breakfast to maintain weight.
- **No Hyperglycemia**
- **Assessment/Plan:** Worsening symptoms warrant total pancreatectomy with splenectomy and islet cell auto-transplantation
Total Pancreatectomy (TP) + Islet Cell Auto-Transplantation (IAT)

- **Goals:**
  - Improve pain and quality of life (TP)
  - Reduce severity of post-surgical Diabetes (IAT)
- **Performed 1st at University of Minnesota in 1977**
- **Procedure for Islet Isolation:**
  - Excise Pancreas
  - Cannulate pancreatic duct
  - Digest pancreatic parenchyma with collagenase
  - Transplant islet cells into the liver via the portal vein with heparin

Rest of History

- **PMHx:**
  - Chronic pancreatitis
  - CFTR mutation
  - Pancreas divisum
  - Hypothyroidism – AB unknown

- **Social Hx:**
  - Lives in Mesa, AZ with parents
  - College graduate
  - Currently unemployed
  - No EtOH, no smoking, no drugs

- **Family Hx:**
  - No history of DM or pancreatic disease.
  - Mother with hypothyroidism.

- **Medications PTA:**
  - Albuterol PRN
  - QVAR nasal spray
  - Zyrtec
  - Flexeril 10mg BID PRN
  - Pepcid 40mg TID
  - Advair BID
  - Morphine 80 mg ER daily
  - Morphine 20 mg q4h PRN
  - Zofran PRN
  - Reglan PRN
  - Lipase-protease-amylase: 4 caps with meals TID
  - Levothyroxine 25 mcg daily
  - Liothyronine 5 mcg PO TID
Pre-Operative Evaluation

- HbA1c (3/2014): 5.4%
- No noted glucose tolerance tests, insulin, or c-peptide levels
- CT Abdomen (performed outside institution)
Body/tail of pancreas taken intra-operatively for islet isolation
- Isolated 236,000 islet-equivalent (IE) in 7 mL of tissue
  - $= 2,145$ IE/kg ($Wt = 110$ kg)
- Islets suspended in transplant media and then infused into the portal vein at the end of the procedure
Post-Operative Plan/Course

- NPO/IVF
- Patient-controlled epidural analgesia for pain control
- NG Tube to low-intermittent suction
- Insulin drip: Goal BG 80-120 mg/dL
  - “Do not stop infusion”
  - Add dextrose if BG < 80 mg/dL

Tachycardia (130’s) and hypotension (70’s/30’s) – improved with 1L LR

Hgb down-trending – total 4 units pRBCs

Febrile 38.6C
• POD #2: Afebrile, VSS, NG tube dc’d
• POD #3: VSS, +nausea, start diabetic clear liquid diet
• POD #4: Consult Endocrine to maintain euglycemia off of the insulin gtt.
Glycemic Control POD #4

- BG Monitoring: Every 1 hour
- BG Range: 96-123 mg/dL
- Insulin gtt: 0.7 units/hr = total 16.8 units/24 hr
- Diet: Clear, liquid; tolerating sugar-free popsicle
- IVF: LR at 100 cc/hr + D5W at 20cc/hr
  - Plan to change to D5 1/2NS at 83 cc/hr
Glycemic Control POD #3-4

Blood Glucose Trend Post-Op Day #4

Hours

Blood Glucose (mg/dL)
Physical Exam

- Vital Signs: T 98.4 F, P 93, BP 114/62, R 20
- Wt: 124.6 kg, Ht 5’ 10”
- Dry Wt: 110 kg, BMI 34.7

- General: appears **uncomfortable** lying supine
- HEET: oropharynx clear, mmm
- Neck: no palpable thyroid or thyroid nodules.
- Cardiac: RRR, no m, **3+ pitting edema to knee**
- Pulmonary: clear to anterior auscultation, good effort.
- Abdomen: bowel sounds present, non-tender. Large bandage across epigastrium clean/dry/in tact
- Neuro: sleepy, but easily arousable. **generalized weakness.**
- Skin: warm, **+dry**, no acanthosis nigricans, no violaceous striae
- Psych: not agitated
Laboratory Studies

- **BMP:**
  - Na 136
  - K 4
  - Cl 105
  - Bicarb 22
  - BUN 8
  - Cr 0.6
  - GFR 110
  - Ca 7.8
  - Mag 1.9
  - Phos 1.8

- **Liver Panel:**
  - TP 4.8
  - Alb 2.8
  - AST 36
  - ALT 36
  - T. bili 2.8
  - Alk Phos 66

- **CBC:**
  - WBC 18.7
  - Hgb 10.2, MCV 90
  - Plt 134
  - Prealbumin – 16 (nl 21-41 mg/dL)
  - TFT’s POD #5:
    - TSH - 4.86
    - Free T4 - 1.24
    - T3 - 64
    - T4 - 6.5
    - rT3 - 1162
Assessment:
- Low insulin requirements
- As diet advances – may require more insulin
- As transplant improves – may require less insulin
- Goal BG per surgery:
  - Pre-prandial: 80-130 mg/dL
  - Post-prandial: < 150 mg/dL

Plan:
- Start Lantus 14 units
- Novolog 1:50 > 130 mg/dL
- D/C insulin drip
- Start prandial Novolog if appetite improves
- Continue D5 1/2NS at 83 cc/hr
- Monitor q1h x 3h -> q2h x 3h then q4h.
- Change to qac/qhs BG as appetite improves
Glycemic Control POD #5-6

Blood Glucose Trend Post-Op Day #5

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:00</td>
<td>120</td>
</tr>
<tr>
<td>17:00</td>
<td>120</td>
</tr>
<tr>
<td>18:00</td>
<td>120</td>
</tr>
<tr>
<td>20:00</td>
<td>120</td>
</tr>
<tr>
<td>22:00</td>
<td>160</td>
</tr>
<tr>
<td>24:00:00</td>
<td>100</td>
</tr>
<tr>
<td>4:00</td>
<td>120</td>
</tr>
<tr>
<td>8:00</td>
<td>120</td>
</tr>
<tr>
<td>12:00</td>
<td>140</td>
</tr>
</tbody>
</table>
Clinical Questions

- What are the short and long-term glycemic goals in patients status-post islet auto-transplantation?
- Based on her clinical features, how long will our patient remain insulin-dependent after islet auto-transplantation?
- What other therapies are available to improve islet cell auto-transplantation outcomes?
Clinical Questions (1)

- What are the short and long-term glycemic goals in patients status-post islet auto-transplantation?
Early Post-Transplant Period

- Neovascularization takes at least 2-4 weeks.
- High rates of beta cell apoptosis in the 1st month (animal model)
  - Worsened under hyperglycemia
- University of Minnesota protocol:
  - Insulin gtt post-operative: BG 100-125 mg/dL
  - Transition to subq insulin at 1 wk: BG 80-125 mg/dL
  - Maintain on insulin therapy for at least 3 months
- Long-term goals:
  - Fasting BG <126 mg/dL
  - PP < 140-180 mg/dL
  - A1c < 6.5%

Clinical Questions (2)

- Based on her clinical features, how long will our patient remain insulin-dependent after islet auto-transplantation?
Insulin-Dependence

Predictive Factors for Islet Autotransplantation

**Positive**
- Islet cell mass
  - Patient factors
  - Isolation technique
- Higher C-peptide/glucose ratio at 1 month post-transplant
- Female

**Negative**
- Degree of pancreatic fibrosis
- History of previous pancreatic resections
- Duration of pancreatitis
- High BMI*


*May be a positive or negative factor*
Islet Function According to Islet Equivalents

### Table 3. Islet Function Status According to Number of Islet Equivalents per Kilogram Transplanted

<table>
<thead>
<tr>
<th>Islet Yield Category</th>
<th>6-Month Follow-up</th>
<th>12-Month Follow-up</th>
<th>24-Month Follow-up</th>
<th>36-Month Follow-up</th>
<th>C-peptide-positive* (&gt;0.6 ng/mL), %</th>
<th>With mean HbA1c &lt;7.0%, †, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,500 IE/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin independent</td>
<td>10 (13)</td>
<td>8 (13)</td>
<td>8 (15)</td>
<td>4 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial function</td>
<td>42 (56)</td>
<td>40 (53)</td>
<td>26 (48)</td>
<td>11 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>23 (31)</td>
<td>27 (36)</td>
<td>20 (37)</td>
<td>18 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,500–5,000 IE/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin independent</td>
<td>16 (20)</td>
<td>19 (23)</td>
<td>19 (31)</td>
<td>8 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial function</td>
<td>64 (78)</td>
<td>60 (72)</td>
<td>37 (60)</td>
<td>23 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>6 (10)</td>
<td>6 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5,000 IE/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin independent</td>
<td>15 (31)</td>
<td>27 (55)</td>
<td>20 (65)</td>
<td>18 (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial function</td>
<td>33 (67)</td>
<td>21 (43)</td>
<td>10 (32)</td>
<td>6 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percent of patients in each islet yield category with C-peptide–positive values >0.6 ng/mL.
†Percent of patients in each islet yield category with mean hemoglobin A1c (HbA1c) levels over time at <7.0%.
IE, islet equivalents.

Insulin Independence by Islet Yield


Fig. 1 Insulin independence by islet yield and duration after islet transplant in autograft recipients at the University of Minnesota (Data from Sutherland et al [8**])
Long-Term Outcomes of Total Pancreatectomy and Islet Auto Transplantation for Hereditary/Genetic Pancreatitis

Srinath Chinnakotla, MD, David M Radosevich, RN, PhD, Ty B Dunn, MD, FACS, Melena D Bellin, MD, Martin L Freeman, MD, Sarah J Schwarzenberg, MD, AN Balamurugan, PhD, Josh Wilhelm, MS, Barbara Bland, MS, RN, Selwyn M Vickers, MD, FACS, Gregory J Beilman, MD, FACS, David ER Sutherland, MD, PhD, Timothy L Pruett, MD, FACS

Table 1. Characteristics of Total Pancreatectomy Islet Autogeneic Transplantation by Hereditary/Genetic and Non—Hereditary/Genetic Causes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hereditary/genetic</th>
<th>Nonhereditary</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary TP-IAT, total, n</td>
<td>80</td>
<td>404</td>
<td></td>
</tr>
<tr>
<td>Transplant era, n (%)</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1996</td>
<td>2 (2.5)</td>
<td>47 (11.6)</td>
<td></td>
</tr>
<tr>
<td>1996 to 2005</td>
<td>12 (15)</td>
<td>72 (17.8)</td>
<td></td>
</tr>
<tr>
<td>2006 to 2012</td>
<td>66 (82.5)</td>
<td>285 (70.5)</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>21.9 ± 1.3</td>
<td>37.9 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n %</td>
<td>47 (58.8)</td>
<td>307 (76.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cause for chronic pancreatitis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary/genetic</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRSS1</td>
<td>38 (47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPINK1</td>
<td>9 (11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFTR</td>
<td>14 (17.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td>19 (23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>34 (8.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>266 (65.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>56 (13.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>48 (11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>22.9 ± 0.7</td>
<td>24.8 ± 0.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Years with pancreatitis, mean ± SD</td>
<td>10.1 ± 1.0</td>
<td>6.4 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years with pain, mean ± SD</td>
<td>11.6 ± 1.1</td>
<td>9.0 ± 0.4</td>
<td>0.016</td>
</tr>
<tr>
<td>Years of narcotic use, mean ± SD</td>
<td>2.6 ± 0.6</td>
<td>3.2 ± 0.2</td>
<td>0.446</td>
</tr>
</tbody>
</table>

CFTR, cystic fibrosis transmembrane conductance regulator; IAT, islet autogeneic transplantation; PRSS1, protease trypsin 1; SPINK1, serine protease inhibitor Kazal type 1; TP, total pancreatectomy.
Table 2. Surgical Characteristics and Background for Total Pancreatectomy Islet Autogeneic Transplantations by Hereditary/Hereditary and Non–Hereditary/Genetic Cause

<table>
<thead>
<tr>
<th></th>
<th>Genetic/hereditary</th>
<th>Nonhereditary</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Primary TP-IAT</td>
<td>80</td>
<td>404</td>
<td></td>
</tr>
<tr>
<td>Total IEQ/kg BW</td>
<td>3,435 ± 361</td>
<td>3,850 ± 128</td>
<td>0.281</td>
</tr>
<tr>
<td>TP</td>
<td>70 (87.5)</td>
<td>337 (83.4)</td>
<td>0.362</td>
</tr>
<tr>
<td>Pancreas fibrosis (0 to 10)</td>
<td>7.0 ± 0.2</td>
<td>4.8 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue volume, mL</td>
<td>9.4 ± 2.4</td>
<td>15.4 ± 1.1</td>
<td>0.021</td>
</tr>
</tbody>
</table>

BW, body weight; IAP, islet autogeneic transplantation; IEQ, islet cell equivalent; TP, total pancreatectomy.
Figure 3. Clinical status for (A) hereditary/genetic and (B) non-hereditary/genetic group by years of total pancreatectomy and islet autograft transplantation (TPIAT) follow-up.
Outcomes: C-peptide and Fasting BG

Figure 4. Prevalence of positive c-peptide (%) in the first year after total pancreatectomy and islet autogeneic transplantation (TPIAT) by hereditary/genetic group.

Figure 5. Fasting glucose (mg/dL) by time after total pancreatectomy and islet autogeneic transplantation (TPIAT) and by hereditary/genetic group.

Outcomes: HbA1c

Figure 6. Hemoglobin A1C (%) by time after total pancreatectomy and islet autogeneic transplantation (TPIAT) and by hereditary/genetic group.

Clinical Questions (3)

• What other therapies are available to improve islet cell auto-transplantation outcomes?
GLP-1 Agonists?

Back to our Patient...

- Post-Op #4: Oxy IR 10 mg po q 4h + 5 mg q4h PRN
- Post-Op Day #8 (day of discharge):
  - 10AM: C-peptide 0.25 pmol/mL (0.75 ng/mL) (no BG at that time)
  - 2PM: BG 131 mg/dL, C-peptide 0.44 pmol/mL (1.32 ng/mL)
  - HbA1c 5.7%
- Post-Op Day #21:
  - Weaned to Lantus 8 units qhs
- Post-Op 2.5 months:
  - Lantus 10 units qhs
  - HbA1c 6%
  - Planning Mixed Meal Tolerance Test
Summary

- Islet cell auto-transplantation appears to lessen the burden of post-surgical diabetes in patients with chronic pancreatitis s/p total pancreatectomy
- Efforts should be made to maintain euglycemia in the acute post-surgical phase for patients with islet cell auto-transplantation
- Degree of insulin-dependence in patients s/p islet cell auto-transplantation is variable and is associated with a number of clinical factors.
Works Cited