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

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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): 1st 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

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Component Results
Component
Test As Ordered
PANCREATITIS PANEL TO AMBRY
Test Requested
PANCREATITIS PANEL TO AMBRY
Result
TEST = PANCREATITS PANEL TO AMBRY
RESULT:
CFTR = KNOWN MUTATION R1162L, NO NOVEL MUTATIONS DETECTED
PRSSI, SPINK1 = NO KNOWN OR NOVEL MUTATIONS DETECTED
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PERFORMED BY AMBRY GENETICS, CA 92656

Hereditary Pancreatitis

- Small subset of cases of chronic pancreatitis
- > 30 known mutations described since 1996
 - Most common mutations: *R122H*, *N291*, *A16V* (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

• <u>Symptoms:</u>

- 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
- <u>Assessment/Plan:</u> 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

Bramis et al. British J Surg. 2012; 99:761-766. Kuroki et al. Surgery Today. 2013; 43:715-719. Matsumoto, S. J Diabetes. 2011;3:328-336.

Rest of History

• <u>PMHx:</u>

- Chronic pancreatitis
 - CFTR mutation
 - Pancreas divisum
- Hypothyroidism AB unknown

• <u>Social Hx:</u>

- 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)

Total Pancreatectomy/Splenectomy and Islet Cell Auto-transplantation 4/2014

- 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



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

- <u>BMP:</u>
 - Na 136
 - K 4
 - Cl 105
 - Bicarb 22
 - BUN 8
 - Cr o.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

- <u>CBC:</u> • 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



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 autotransplantation?
- 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 %

Bellin et al. Curr Diab Rep 2012; 12:580-586.

Clinical Questions (2)

 Based on her clinical features, how long will our patient remain insulin-dependent after islet autotransplantation?

Insulin-Dependence



Sutherland et al. J Am Coll Surg 2012;214:409-426.

Predictive Factors for Islet Autotransplantation

Positive

- Islet cell mass
 - Patient factors
 - Isolation technique
- Higher C-peptide/glucose ratio at 1 month posttransplant
- Female

<u>Negative</u>

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

Bramis et al. British J Surg. 2012; 99:761-766. Bellin et al. Curr Diab Rep 2012; 12:580-586.

*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

- 22/12	6-Month follow-up		12-Month follow-up		24-Month follow-up		36-Month follow-up		C-peptide-positive*	With mean HbA1c
	n	%	n	%	n	%	n	%	(>0.6 ng/mL), %	< 7.0% , [†] %
<2,500 IE/kg	75		75		54		33		79	71
Insulin independent	10	13	8	13	8	15	4	12		
Partial function	42	56	40	53	26	48	11	33		
Insulin dependent	23	31	27	36	20	37	18	55	-	
2,500-5,000 IE/kg	82		83		62		37		97	86
Insulin independent	16	20	19	23	19	31	8	22		
Partial function	64	78	60	72	37	60	23	62		
Insulin dependent	2	2	4	5	6	10	6	16		
>5,000 IE/kg	49		49		31		25		100	94
Insulin independent	15	31	27	55	20	65	18	72		
Partial function	33	67	21	43	10	32	6	24		
Insulin dependent	1	2	1	2	1	3	1	4		

*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.

Sutherland et al. J Am Coll Surg 2012;214:409-426.

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••])

Sutherland et al. J Am Coll Surg 2012;214:409-426.

Long-Term Outcomes of Total Pancreatectomy and Islet Auto Transplantation for Hereditary/Genetic Pancreatitis

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Table	1.	Characteristics	of	Tota	Pancre atectomy	Islet
Autoge	neic	Transplantatio	n	by H	lereditary/Genetic	and
Non-H	lered	litary/Genetic Ca	aus	es		

Characteristic	Hereditary/genetic	c Nonhereditary	p Value
Primary TP-IAT,			
total, n	80	404	
Transplant era,			
n (%)			0.028
Before 1996	2 (2.5)	47 (11.6)	
1996 to 2005	12 (15)	72 (17.8)	
2006 to 2012	66 (82.5)	285 (70.5)	
Age, y, mean ± SD	21.9 ± 1.3	37.9 ± 0.6	< 0.001
Female sex, n %	47 (58.8)	307 (76.0)	0.002
Cause for chronic pancreatitis, n (%)	ND		5.5
Hereditary/genetic			NA
PRSS1	38 (47.5)		
SPINK1	9 (11.3)		
CFTR	14 (17.5)		
Familial	19 (23.8)		
Alcohol		34 (8.4)	
Idiopathic		266 (65.8)	
Pancreas divisum	1	56 (13.9)	
Other	1 A 1	48 (11.9)	
Body mass index,			
mean ± SD	22.9 ± 0.7	24.8 ± 0.3	0.009
Years with			
pancreatitis,			
mean \pm SD	10.1 ± 1.0	6.4 ± 0.3	< 0.001
Years with pain, mean ± SD	11.6 ± 1.1	9.0 ± 0.4	0.016
Years of narcotic use,			
mean \pm SD	2.6 ± 0.6	3.2 ± 0.2	0.446

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

	Genetic/hereditary	Nonhereditary	p value
Number of Primary			
TP-IAT	80	404	
Total IEQ/kg BW	$3,435 \pm 361$	3,850 ± 128	0.281
TP	70 (87.5)	337 (83.4)	0.362
Pancreas fibrosis	DIOI		
(0 to 10)	7.0 ± 0.2	4.8 ± 0.1	< 0.001
Tissue volume, mL	9.4 ± 2.4	15.4 ± 1.1	0.021
BW, body weight; IAl equivalent; TP, total pa	P, islet autogeneic tran increatectomy.	splantation; IEQ,	islet cell



Outcomes: C-peptide and Fasting BG





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?



Wang et al. Curr Diab Rep 2013;13:723-732.

Modulate immunoregulation and inflammatory reaction

Back to our Patient...

- Post-Op #4: Oxy IR 10 mg po q 4h + 5 mg q4h PRN
- Post-Op #5: Wean PCEA DC'd Post-Op #7.
- 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

- Bellin et al. "No Islets Left Behind: Islet Autotransplantation for Surgery-Induced Diabetes." Curr Diab Rep 2012; 12:580-586.
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