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Type 1 diabetes mellitus in patients with recurrent acute and chronic pancreatitis: a case series

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Abstract

Background/Objectives: Pancreatogenic diabetes mellitus has been assumed to result from **non-immune** beta cell destruction when the pancreas is replaced by fibrotic tissue secondary to acute and chronic pancreatitis. We hypothesize that recurrent episodes of pancreatic inflammation may increase the risk for developing β-cell autoimmunity in susceptible individuals.

Methods: We describe 11 patients who had both recurrent acute and/or chronic pancreatitis and type 1 diabetes (T1D) requiring insulin therapy.

Results: All 11 patients had positive autoantibodies and 8 patients tested had minimal to undetectable (7/8) or moderate (1/8) stimulated C-peptide at 12 months after T1D onset. Three had biopsy confirmation of insulitis.

Conclusions: These cases lend support to the theory that pancreatitis may increase risk for T1D. We postulate that the pro-inflammatory conditions of pancreatitis may increase posttranslational protein modifications of β-cell antigens and neoepitope generation, which are potential initiating events for loss of β-cell self-tolerance.

Keywords

Pancreatogenic Diabetes; Type 1 Diabetes; Pancreatitis; Autoimmunity

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Introduction

Patients with recurrent acute and chronic pancreatitis have an increased risk for diabetes mellitus (DM), diagnosed as pancreatogenic DM (or “Type 3c” DM) (1). Pancreatogenic DM results from islet damage and loss from pancreatic inflammation and fibrosis, without β-cell autoimmunity. However, we have observed more cases of type 1 diabetes (T1D) in our pancreatitis clinic than we would expect based on the general population prevalence of T1D of about 1 in every 400 persons (2). Herein, we report 11 cases from our clinic with both recurrent acute pancreatitis or chronic pancreatitis and T1D. We postulate that recurrent episodes of pancreatic inflammation may increase the risk for developing β-cell autoimmunity in susceptible individuals.

Methods

We retrospectively reviewed medical records data for 11 patients who were seen by our specialty pancreatitis group at M Health Fairview at the University of Minnesota between 2008 and 2019 for medical care who had both pancreatitis and Stage 3 or 4 T1D (requiring insulin), supported by positive β-cell autoantibodies (AAbs), loss of C-peptide production, and/or pancreatic histology. β-cell antibodies were collected for islet cell, glutamic acid decarboxylase (GAD), and insulin antibodies in all patients, with islet tyrosine phosphatase 2 (IA-2) and zinc transporter 8 (ZnT8) antibodies also collected in some, depending on clinical availability at time of assessment. Mixed meal tolerance testing was performed for C-peptide levels when clinically indicated; in this test, C-peptide levels collected fasting and stimulated after 6mL/kg to maximum of 360 mL Boost High Protein. Histology samples were obtained from a pancreatic biopsy in surgical patients and were reviewed by a trained pathologist. The samples were immunohistochemically stained for CD3, synaptophysin and insulin to detect insulitis. Summary data are presented as median and range. The study was approved by the University of Minnesota Institutional Review Board.

Results

Clinical characteristics for each case are reported in Table 1. Patients had a median age of 13 years (range 1–43 years) at first pancreatitis diagnosis and 15 years (range 4 – 46 years) at T1D diagnosis. All had positive β-cell autoantibodies: 1 AAb in one case, 2 AAbs in 5 cases, and ≥3 AAbs in 5 cases. Eight patients had mixed meal tolerance testing (Boost HP, 6mL/kg to 360 mL) performed as part of surgical protocols, with 7 of 8 having low to undetectable C-peptide, and 1 patient having moderate C-peptide at 12 months after T1D onset, but requiring meal time insulin dosing via insulin pump. C-peptide testing was not performed in 3 patients but 3 AAbs were positive in each of these cases.

Seven patients were diagnosed with T1D as a child, while 4 were adults age 30–46 years. Pancreatitis diagnosis preceded the T1D diagnosis in 10/11 cases. For 1 case, recurrent acute pancreatitis was formally diagnosed after T1D onset; this patient also had a complex past medical history of hematopoetic stem cell transplant for Diamond-Blackfan anemia (Case 2). Most patients (n=8) in our cohort had both recurrent acute pancreatitis and chronic

pancreatitis confirmed. The only 2 patients without confirmed acute pancreatitis (Cases 1,9) had a history of episodic abdominal pain suggestive of undiagnosed acute pancreatitis. Case 1 was diagnosed with chronic pancreatitis after several years of recurrent abdominal pain episodes. Case 9 was diagnosed with autosomal dominant hereditary pancreatitis (PRSS1) as an adult after her child was diagnosed with PRSS1, and in retrospect had several episodes of abdominal pain as a child. Chronic pancreatitis was also evident by imaging and/or histopathology in 9 cases.

In 7 cases, total pancreatectomy with islet autotransplant (TPIAT) was performed for management of pancreatitis. Type 1 diabetes is classically a contraindication to islet transplant. However, 2 cases (Case 5, 8) developed evidence of T1D only after TPIAT, 4 cases had AAbs+ pre-TPIAT but were otherwise normoglycemic (Case 1,6,10,11) before surgery, and 1 case had AAbs+ and was on insulin but with high C-peptide pre-TPIAT. With the exception of Case 11, these patients progressed to minimal to no islet function post TPIAT. Three surgical cases (Case3, 6 & 11) also had evidence of insulitis on immunohistochemistry.

Discussion

Herein we report 11 patients diagnosed with both T1D and pancreatitis presenting to our institution for medical or surgical care. These patients were deemed to have T1D, rather than classic pancreatogenic DM, based on positive AAbs in all cases, with low C-peptide documented in the majority. Immunohistochemical stains also showed evidence of insulitis in 3 cases. Pancreatitis was diagnosed first, prior to T1D in 10/11 cases. In T1D, insulin deficiency results from targeted autoimmune destruction of the islet β-cells. This autoimmunity is triggered by unknown environmental exposures in genetically susceptible individuals (3). Acute pancreatitis is characterized by inflammation and injury of the exocrine component of the pancreas. We postulate that pancreatic tissue injury and inflammation of pancreatitis may activate β-cell autoimmunity in a subset of patients with pancreatitis.

To our knowledge this is the first report to describe a series of patients with co-existing T1D and pancreatitis. However, the concept that pancreatic injury could be a trigger for β-cell autoimmunity is of recent scientific interest. In the International Study Group for Pediatric Pancreatitis: In Search for a Cure (INSPPIRE), a registry study which enrolls children with recurrent acute pancreatitis or chronic pancreatitis, 20% of all children with DM had positive β-cell autoantibodies (4). Our group has also previously reported a case of de novo T1D after TPIAT (case 8) (5), which at the time was thought to be an isolated case. With accumulation of new data, we now suspect an association of T1D and pancreatitis. A unique feature to this report is our ability to access to histology which showed evidence of insulitis characteristic for T1D in 3 cases. Variable timing between surgery and T1D onset, and sampling bias with limited tissue may explain variability in histopathology and lack of observed insulitis in the remaining cases.

While it is not yet known if T1D is driven by self-antigens or neoantigens, there is increasing evidence that posttranslational protein modifications of β-cell antigens and

generation of neoepitopes are initiating events in loss of β-cell self-tolerance (6, 7). Importantly, the risk factors to incite posttranslational protein modification and neoepitope generation include pro-inflammatory cytokines, reactive oxygen species, and increased endoplasmic reticulum stress—conditions that may be precipitated in the setting of acute pancreatitis (6, 8).

Of note, in our cohort, 5 of the 11 patients carried a gene mutation in the cationic trypsinogen gene (*PRSS1*) which is causative for a rare form of autosomal dominant hereditary pancreatitis (9). In this condition, acute pancreatitis typically occurs in childhood, with a mean age for onset of symptomatic disease of 11 years. Most patients in this series underwent pancreatectomy alone or TPIAT, but this likely represents sampling bias in our population as the University of Minnesota has a large surgical program for pancreatitis.

This is a case series and thus no definite conclusions can be made. We also do not have additional data on genetic risk factors for T1D for this patient population. However, we believe these cases lend support to the theory that pancreatitis may increase risk for T1D in otherwise susceptible individuals. The National Institutes of Health has very recently established a “Type 1 Diabetes and Acute Pancreatitis” research consortium to study the potential overlap between pancreatitis and T1D. Further research will be needed to confirm observations and elucidate mechanisms that may increase risk for T1D in pancreatitis.

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Table 1:

Clinical history for pancreatitis and diabetes for each case

Case	AP	CP	Age (y) AP or CP Dx	Age (y) T1D Dx	Genetic Risk Factors*	Pancreas Surgery	Age (y) Pancreas Surgery	Insulitis by Biopsy	GAD Ab	Insulin Ab	Islet Cell Ab	IA-2 Ab	ZnT8 Ab	C-peptide fasting/ stimulated (ng/mL)*	Duration T1D at C-peptide (months)	HbAlc range (%)	Current insulin regimen
1	Suspected	Yes	43	46	N/A	TPIAT	46	No	+	-	-	-	ND	0.1/0.1	13	5.4 – 8.3	insulin pump
2	Yes	Yes	13	9	N/A	TP without IAT	15	No	+	+		ND	ND	0.1/0.1 **	68	7.8 – 10.6	insulin pump
3	Yes	Yes	10	15	N/A	TPIAT	17	Yes	+	+	+	+	-	0.1/0.1	41	5.1 – 6.9	insulin pump
4	Yes	No	13	14	PRSS1 (R122H)	None	N/A		+	+	+	ND	ND	ND		5.3 – 10.3	insulin pump
5	Yes	Yes	9	16	N/A	TPIAT	15	No	+	+	-	ND	ND	0.2/0.7	19	4.8 – 9.3	insulin pump
6	Yes	Yes	2	7	PRSS1 (R122H) + CFTR (R75Q)	TPIAT	7	Yes	+	+				0.1/0.1	3	5.0 – 8.4	insulin pump
7	Yes	Yes	1	10	PRSS1 (R122H)	TP without IAT	12	No	+	+		+	ND	ND		7.1 – 8.5	insulin pump
8	Yes	Yes	37	44	N/A	TPIAT	43	No	+	+				0.1/0.1	8	5.2 – 12.8	MDI
9	Suspected	No	33	33	PRSS1 (R122H)	None	N/A		+		+	+	ND	ND		5.9 – 9.9	MDI
10	Yes	Yes	27	30	CFTR ((TG)12-5T variant)	TPIAT	30	No	+	+	+		ND	0.1/0.3	6	4.6 – 9.2	insulin pump
11	Yes	Yes	1	4	PRSS1 (R122H)	TPIAT	4	Yes	+	+	-	-	-	0.6/2.0	12	5.1 – 6.4	insulin pump

AP=acute pancreatitis, CP= chronic pancreatitis, T1D = type 1 diabetes mellitus, Dx=diagnosis; GAD = Glutamic Acid Decarboxylase; IA-2 = islet tyrosine phosphatase 2; ZnT8= zinc transporter 8; MDI= multiple daily injections; TPIAT= total pancreatectomy and islet autotransplant; N/A = not applicable; ND= not done

+ indicates genetic risk factors for pancreatitis

* fasting and stimulated C-peptide value by Boost HP meal (6 mL/kg to maximum 360 mL), most recent result

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** C-peptide level before total pancreatectomy without islets.