ORIGINAL ARTICLE

Silent Celiac Disease Activated by Pancreaticoduodenectomy

**John T. Maple · Randall K. Pearson ·
Joseph A. Murray · Darlene G. Kelly · Luis F. Lara ·
Andy C. Fan**

Abstract Diarrhea and weight loss are common after pancreaticoduodenectomy, and arise from varying etiologies. An uncommon but important cause for these symptoms is the postoperative activation of silent celiac disease. We sought to describe the clinical presentation, diagnosis, treatment, and follow-up of a series of patients with silent celiac disease unmasked after pancreaticoduodenectomy, and to summarize the existing case reports on this association. A search of the electronic medical record at our institution was performed cross-referencing terms associated with celiac disease and pancreaticoduodenectomy for the years 1976–2004. Cases were then reviewed to ensure that no signs or symptoms attributable to celiac disease were present preoperatively. Seven patients were identified; five were male, and the median age was 56. All patients underwent surgery for a presumed pancreatic or ampullary malignancy. Six patients developed symptoms ultimately attributable to celiac disease immediately after pancreaticoduodenectomy, most commonly diarrhea and weight loss. A single patient had silent celiac disease incidentally diagnosed at pancreaticoduodenectomy that remained silent postoperatively on an unrestricted diet. Symptoms completely resolved in 4 of 6 patients after initiation of a gluten-free diet, with partial improvement in the remaining 2 patients. The median delay from pancreaticoduodenectomy to diagnosis of celiac disease in the 6 symptomatic patients was 6 months. Clinicians should consider celiac disease as a potential diagnosis in patients with failure to thrive and diarrhea after pancreaticoduodenectomy. This entity is uncommon, but may be underrecognized. The underlying mechanism may relate to an increased antigenic load secondary to postsurgical changes in intestinal physiology.

Keywords Pancreaticoduodenectomy · Celiac disease · Diarrhea · Post-operative complications

J. T. Maple (✉) · R. K. Pearson · J. A. Murray · D. G. Kelly ·
L. F. Lara · A. C. Fan
Department of Gastroenterology, Washington University,
660 South Euclid Avenue, Campus Box 8124, St. Louis,
Missouri 63110
e-mail: jmaple@im.wustl.edu

Patients commonly experience diarrhea and weight loss after pancreaticoduodenectomy for a variety of reasons, including pancreatic exocrine insufficiency and changes in bile salt metabolism [1]. In many cases these symptoms are transient, and may improve with pancreatic enzyme supplementation and other conservative measures. However, rarely this constellation of symptoms heralds the unmasking of overt celiac symptoms in patients previously affected with either silent or latent celiac disease [2].

Celiac disease is characterized by damage to the proximal small bowel owing to an immunologic intolerance to gluten, a protein commonly found in wheat, barley, and rye grains. Occurring most commonly in people of Caucasian background, celiac disease requires the genetic milieu of certain HLA alleles (DQ-2, and less commonly DQ-8) to occur. However, despite the ubiquitous nature of gluten, only a minority of patients with the HLA predisposition to develop celiac disease actually does, and other yet-to-be-identified genes and/or environmental triggers may play a role [3]. The "classic" presentation of celiac disease with malabsorption and steatorrhea beginning in childhood is now uncommon, and more patients are now diagnosed in adulthood [4, 5]. Of those who present with gastrointestinal symptoms, the onset of symptoms has been correlated in some cases to a "trigger," such as pregnancy or surgery [6, 7].

The unmasking of silent or latent celiac disease has been reported after upper gastrointestinal surgery including

esophageal and gastric resection [7, 8]. Celiac disease manifesting after pancreaticoduodenectomy is uncommon, but has also been reported [2, 9–13]. In this report, we describe 6 cases of celiac disease unmasked by pancreaticoduodenectomy and a single case of silent celiac disease diagnosed histologically at pancreaticoduodenectomy that remained symptomatically silent postoperatively (patient 7). This report also summarizes the existing case reports on this association, and discusses potential mechanisms that may underlie this phenomenon.

Methods

A search of the electronic Mayo medical record was performed cross-referencing the terms "celiac disease," "sprue," "celiac sprue," "non-tropical sprue," and "gluten-sensitive enteropathy" against the terms "pancreaticoduodenectomy" and "Whipple's operation" for the years 1976–2004, and ultimately yielded the 7 cases described in this report. In each of the 7 cases, no signs or symptoms attributable to celiac disease (e.g., diarrhea, microcytic anemia, fat-soluble vitamin deficiency) preceded the pancreaticoduodenectomy. The first 3 cases were evaluated before endomysial antibodies or tissue transglutaminase antibodies were clinically available.

Results

Patient characteristics

Demographic and clinical characteristics of the 7 patients are summarized in Table 1. Five of the patients were male, and the median age was 56. All patients underwent surgery for a presumed pancreatic or ampullary malignancy, although in 2 cases of suspected pancreatic head cancer, no malignancy was demonstrated on pathologic sectioning. In 5 of the 7 patients, villous atrophy and intraepithelial lymphocytosis were present in the duodenal mucosa not involved by tumor at the time of pancreaticoduodenectomy; in 1 case only "chronic inflammation" was commented on, and in 1 case no mention was made of the duodenal mucosa. For patients 1–6, symptoms ultimately attributable to celiac disease began immediately or within weeks after pancreaticoduodenectomy, with diarrhea and weight loss being the most commonly reported symptoms. The median weight loss among these 6 patients was 10 kg, and 3 patients (1, 2, and 4) required temporary support with parenteral nutrition.

For patient 7, duodenal mucosal changes compatible with celiac disease were recognized at the time of pancreaticoduodenectomy. However, his recovery from pancreaticoduodenectomy was uneventful, with modest early weight loss quickly abating, and no gastrointestinal symptoms ever

Table 1 Clinical features of 7 patients with celiac disease manifesting only after pancreaticoduodenectomy

Patient	Age at pancreaticoduodenectomy, gender	Indication for pancreaticoduodenectomy	Duodenal histology, pancreaticoduodenectomy[b]	Celiac disease timing	Celiac disease symptoms/signs
1	67 M	Mass in the head of the pancreas[a]	2, 3 ,5	Immediate	Diarrhea (steatorrhea), weight loss, abdominal pain
2	39 M	Pancreatic mucinous cystadenocarcinoma (head)	5	Immediate	Diarrhea (steatorrhea), osteomalacia
3	71 F	Ampullary adenocarcinoma	Unknown	2 weeks	Diarrhea, weight loss
4	65 M	Pancreatic adenocarcinoma (head)	1, 3	Immediate	Diarrhea, weight loss
5	55 M	Mass in the head of the pancreas[a]	2, 3, 4, 5	"Weeks"	Diarrhea (steatorrhea), weight loss
6	56 F	Ampullary carcinoid tumor	1,3	Immediate	Diarrhea, weight loss, nausea, bloating
7	55 M	Pancreatic adenocarcinoma (head)	1, 3, 4, 5	? Any CD sx	Mild weight loss

[a]No malignancy on pathology.

[b]1 - total villous atrophy, 2 - subtotal villous atrophy, 3 - intraepithelial lymphocytosis, 4 - crypt hyperplasia, 5 - chronic inflammation.

Table 2 Laboratory and pathologic features of 7 patients with celiac disease manifesting only after pancreaticoduodenectomy

| Patient | Histology[a] | Basis for diagnosis of celiac disease[b] | | | Symptomatic response to gluten-free diet |
		Tissue transglutaminase antibodies	Endomysial antibodies	Gliadin	
1	2, 3, 5				Partial response
2	1, 3				Complete response, notable worsening with gluten rechallenge
3	2				Partial response
4	2, 3			89.2 EU	Eventual complete response
5	2, 3, 4, 5	75.4 U	1:80		Eventual complete response
6	1, 3	145.3 U	1:5120		Complete response
7	NA	>250 U	1:1280		Weight loss abated, never used gluten-free diet as pt asymptomatic

[a]Histology on *repeat* small bowel biopsies. 1 - total villous atrophy, 2 - subtotal villous atrophy, 3 - intraepithelial lymphocytosis, 4 - crypt hyperplasia, 5 - chronic inflammation.

[b]TTG - serum tissue transglutaminase antibody, IgA (normal ≤ 20 U); EMA - serum endomysial antibodies, IgA (normal negative); Gliadin - serum gliadin antibody; IgA (normal <50 EU).

occurring despite a gluten-containing diet. Over 2 years of follow-up, he enjoyed good health, with no diarrhea, anemia, or evidence of malabsorption. Two years after pancreaticoduodenectomy, serologic markers for celiac disease were checked and found to be strongly positive (Table 2). Mild transaminase elevations were attributed to a radiographic fatty liver, or less likely to celiac disease, and the patient elected to continue an unrestricted diet and clinical observation.

Diagnosis of celiac disease

Patients 1–6 underwent further medical evaluation as a result of their symptoms, which led to the diagnosis of celiac disease. The laboratory and pathologic data providing the basis for the diagnosis of celiac disease in these patients is summarized in Table 2. Patients 1–6 all had repeat small bowel biopsies demonstrating villous atrophy, most with prominent intraepithelial lymphocytosis also. Serologic testing was clinically available during the time period in which patients 4–6 were evaluated (in addition to patient 7); at least 1 marker was positive in each of these patients. Symptoms completely resolved in 4 of 6 patients after initiation of a gluten-free diet, with a partial improvement seen in the remaining 2 patients. Figure 1 demonstrates intestinal histopathology in patient 4 before and after initiation of a gluten-free diet.

It can be clearly ascertained that the histologic diagnosis of celiac disease was apparent in the pancreaticoduodenectomy specimen in 2 cases (1 and 5), yet not reported by the pathologist. This may have been the case in patients 2 and 3, although this is less certain, because the original pancreaticoduodenectomy tissue blocks were not reviewed in our institution. For patients 4 and 6, the original pancreaticoduodenectomy pathology report detailed villous atrophy and intraepithelial lymphocytosis, yet the clinical significance of
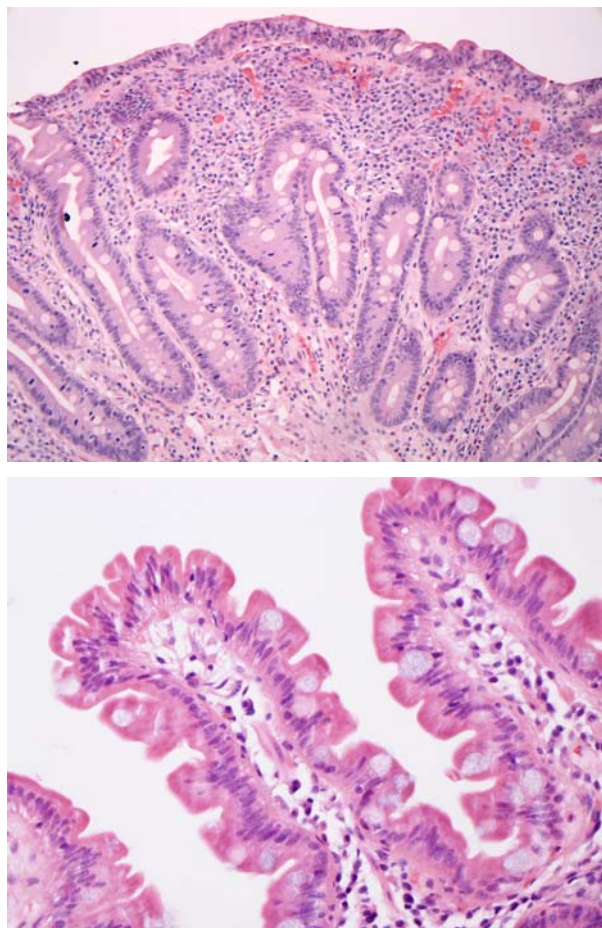

Fig. 1 **a** Duodenal histopathology in patient 4 at the time of diagnosis of celiac disease, with villous atrophy and intraepithelial lymphocytosis (200× magnification). **b** Jejunal histopathology in patient 4 after eleven months on a gluten-free diet, with healthy, normal-appearing villi (400× magnification)

these findings was not appreciated by the treating clinicians. The median delay from pancreaticoduodenectomy to diagnosis of celiac disease in patients 1–6 was 6 months.

Discussion

Diarrhea and weight loss are common after pancreaticoduodenectomy. Preoperative weight loss of 5–10 kg with pancreatic and ampullary malignancies is common, and postoperative weight loss of another 5–8 kg is typical, with the weight often stabilizing by 6 months after surgery in the absence of cancer recurrence [1, 14]. Diarrhea after pancreaticoduodenectomy is frequently encountered and may be multifactorial. Steatorrhea from exocrine insufficiency [1], accelerated colonic transit from altered bile salt metabolism [15], and the loss of inhibitory tone on intestinal motor function from sympathetic denervation are all potential diarrheal mechanisms after pancreaticoduodenectomy [16]. Empiric pancreatic enzymes and loperamide are reasonable in the initial management of these patients. However, when diarrhea and weight loss persist, clinicians should consider the emergence of previously silent or latent celiac disease.

Patients who have normal small bowel mucosa while ingesting an unrestricted diet, but later develop celiac disease had latent celiac disease. Patients who have mucosal atrophy and corroborating celiac serologies, yet no symptoms (e.g., an asymptomatic family member of a celiac patient who undergoes screening) have silent celiac disease [5]. Historically, celiac disease has been reported to emerge after various upper gastrointestinal surgeries [7, 8]. Other triggers, including pregnancy and enteric infections, may influence the emergence and activity of celiac disease [6, 17]. In these reports, the unmasking of silent celiac disease is more common than the triggering of latent celiac disease.

Celiac disease unmasked by pancreaticoduodenectomy was first reported by MacGowan et al. [2] in 2 patients, with 5 subsequent reports each describing a single case [9–13]. Including these 7 new cases from our institution, 14 reports of this phenomenon have now been described. Among all reported cases, an ampullary or duodenal adenocarcinoma was the most common indication for pancreaticoduodenectomy, occurring in 8 of 14 patients. Although pancreatic adenocarcinoma is a much more common indication for pancreaticoduodenectomy than ampullary or duodenal adenocarcinoma, patients with celiac disease are at heightened risk for these malignancies [18]. In 12 of 14 patients, the pancreaticoduodenectomy surgical pathology report was available, and thus the histology from the duodenum not involved by tumor is known. Of these 12, just 1 specimen showed normal histology [11]; thus, pancreaticoduodenectomy appears to activate silent celiac disease much more commonly than latent celiac disease. Patient 7 from our institution is the lone example

of silent celiac disease that remained silent postoperatively on an unrestricted diet. Celiac disease is a premalignant condition [19], and care must be taken by pathologists and clinicians to identify and appropriately treat celiac disease when present on pancreaticoduodenectomy specimens; in our series, a delay in diagnosis was unfortunately common.

The mechanism for the unmasking of celiac disease after pancreaticoduodenectomy is not known. One potential explanation is that transient bowel hyperpermeability following upper gut surgery leads to a heightened gluten challenge. Intestinal permeability as measured by the dual sugar test (lactose and mannitol) is increased after any gut surgery [20, 21]; paracellular absorption is disproportionately increased as compared with the transcellular route. It has recently been demonstrated that zonulin (a human protein analogue of the *Vibrio cholerae* zonula occludens toxin) mediates intestinal tight junction function (and thus paracellular solute transit) [22], and that zonulin expression is increased in active celiac disease [23]. Thus, any disruption of the intestinal mucosal barrier and tight junction function allows enhanced paracellular delivery of gluten peptides to the lamina propria [24]. In susceptible patients with silent or latent celiac disease, the resultant challenge may stimulate the innate and adaptive immune response enough to result in clinically apparent inflammatory intestinal disease.

In summary, clinicians should consider celiac disease as a potential diagnosis in patients with failure to thrive and diarrhea after pancreaticoduodenectomy. This entity is uncommon, but may be underrecognized. The underlying mechanism may relate to an increased antigenic load secondary to postsurgical changes in intestinal physiology.

References

1. Nguyen TC, Sohn TA, Cameron JL, Lillemoe KD, Campbell KA, Coleman J, Sauter PK, Abrams RA, Hruban RH, Yeo CJ (2003) Standard vs. radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective, randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. J Gastrointest Surg 7:1–11
2. MacGowan DJL, Hourihane DO, Tanner WA, O'Morain C (1996) Duodeno-jejunal adenocarcinoma as a first presentation of coeliac disease. J Clin Pathol 49:602–604
3. Kagnoff MF (2005) Overview and pathogenesis of celiac disease. Gastroenterology 128:S10–S18
4. Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ (2003) Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. Clin Gastroenterol Hepatol 1:19–27
5. Dewar DH, Ciclitira PJ (2005) Clinical features and diagnosis of celiac disease. Gastroenterology 128:S19–S24

6. Malnick SD, Atali M, Lurie Y, Fraser G, Geltner D (1998) Celiac disease presenting during the puerperium: a report of three cases and a review of the literature. J Clin Gastroenterol 26:164–166

7. Bai J, Moran C, Martinez C, Niveloni S, Crosetti E, Sambuelli A, Boerr L (1991) Celiac sprue after surgery of the upper gastrointestinal tract. Report of 10 cases with special attention to diagnosis, clinical behavior, and follow-up. J Clin Gastroenterol 13:521–524

8. Hedberg CA, Melnyk CS, Johnson CF (1966) Gluten enteropathy appearing after gastric surgery. Gastroenterology 50:796–804

9. Mason CH, Dunk AA (1997) Duodeno-jejunal adenocarcinoma and coeliac disease. J Clin Pathol 50:619

10. Gebrayel N, Conlon K, Shike M (2000) Coeliac disease diagnosed after pancreaticoduodenectomy. Eur J Surg 166:742–743

11. Boggi U, Bellini R, Rosetti E, Pietrabissi A, Mosca F (2001) Untractable diarrhea due to late onset celiac disease of the adult following pancreaticoduodenectomy. Hepatogastroenterology 48:1030–1032

12. Stone CD, Klein S, McDoniel K, Davidson NO, Prakash C, Strasberg SM (2005) Celiac disease unmasked after pancreaticoduodenectomy. JPEN J Parenter Enteral Nutr 29:270–271

13. Chedid AD, Kruel CRP, Chedid MF, Torresini RJS, Geyer GR (2005) Development of clinical celiac disease after pancreatico-duodenectomy: a potential complication of major upper abdominal surgery. Langenbecks Arch Surg 390:39–41

14. Tran KTC, Smeenk HG, van Eijck CHJ, et al (2004) Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg 240:738–745

15. Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR (1996) Bowel habit after cholecystectomy: physiological changes and clinical implications. Gastroenterology 111:617–622

16. Chang EB, Fedorak RN, Field M (1986) Experimental diabetic diarrhea in rats. Intestinal mucosal denervation hypersensitivity and treatment with clonidine. Gastroenterology 91:564–569

17. Carroccio A, Cavataio F, Montalto G, Paparo F, Troncone R, Iacono G (2001) Treatment of giardiasis reverses "active coeliac disease to "latent" celiac disease. Eur J Gastroenterol Hepatol 13:1101–1105

18. Askling J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbom A (2002) Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology 123:1428–1435

19. West J, Logan RF, Smith CJ, Hubbard RB, Card TR (2004) Malignancy and mortality in people with coeliac disease: population based cohort study. BMJ 329:716–719

20. Matejovic M, Krouzecky A, Rokyta R, Treska V, Spidlen V, Novak I (2004) Effects of intestinal surgery on pulmonary, glomerular, and intestinal permeability, and its relation to the hemodynamics and oxidative stress. Surg Today 34:24–31

21. Holland J, Carey M, Hughes N, Sweeney K, Byrne PJ, Healy M, Ravi N, Reynolds JV (2005) Intraoperative splanchnic hypoperfusion, increased intestinal permeability, down-regulation of monocyte class II major histocompatibility complex expression, exaggerated acute phase response, and sepsis. Am J Surg 190:393–400

22. Fasano A, Uzzau S, Fiore C, Margaretten K (1997) The enterotoxic effect of zonula occludens toxin (Zot) on rabbit small intestine involves the paracellular pathway. Gastroenterology 112:839–846

23. Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE (2000) Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet 355:1518–1519

24. Ciccocioppo R, Di Sabatino A, Corazza GR (2005) The immune recognition of gluten in coeliac disease. Clin Exp Immunol 140:408–416