

CASE REPORT

Elevated Deoxycholic Acid and Idiopathic Recurrent Acute Pancreatitis: A Case Report With 48 Months of Follow-up

Gregory A. Plotnikoff, MD, MTS, FACP, *United States*

Author Affiliation

Penny George Institute
for Health and Healing,
Abbott Northwestern
Hospital, Minneapolis,
Minnesota.

Correspondence

Gregory A. Plotnikoff,
MD, MTS, FACP
Gregory.plotnikoff
@allina.com

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ABSTRACT

Recurrent pancreatitis is a potentially life-threatening condition with a well-established differential diagnosis. In a significant number of cases, no explanation exists. This case report documents one patient with a clear pattern of recurrent acute pancreatitis and no identifiable cause despite great effort. After 7 years of recurrent symptoms, she was found to have marked elevation of fecal deoxycholic acid (DCA), a secondary bile acid used to precipitate pancreatitis in animal models. This report documents cessation of symptoms/hospitalizations with normalization of her fecal DCA levels. This secondary bile acid is easily measured in stool. Needed now is an observational study of fecal DCA levels in patients with recurrent acute pancreatitis.

PRESENTING CONCERNS

The subject of this report is a 56-year-old white, married, non-drinking, non-smoking female health professional referred to the Penny George Institute for Health and Healing (Minneapolis, Minnesota) in March of 2009 for evaluation of 7 years of idiopathic recurrent acute pancreatitis requiring numerous hospitalizations. Previous specialized evaluations included endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and magnetic resonance cholangiopancreatography (MRCP). These demonstrated normal pancreatic morphology and normally sized ducts with no dilation or structuring within the main pancreatic duct or any side branches. Also demonstrated were normal intra- and extra-hepatic bile ducts and possible mild diffuse fatty infiltration of the liver. Her laboratory evaluations were negative for elevated baseline transaminases, calcium, triglycerides, and autoimmune markers. Her IgG subclass 4 was normal.

CLINICAL FINDINGS

The patient noted episodes of abdominal pain that began in 2000 after beginning the proton pump inhibitor rabeprazole for intermittent dyspepsia. At that time, she reported multiple intermittent episodes of sharp epigastric pain lasting from 30 to 60 minutes. These were attributed to her gallbladder, and she underwent an uneventful laparoscopic cholecystectomy. This surgery failed to relieve her abdominal discomfort.

She was then evaluated for possible biliary disease and underwent ERCP with sphincterotomy. Neither stones nor biliary sludge were found. This procedure precipitated her first hospitalization for pancreatitis. Following this, from 2002 to March of 2009, she experienced severe abdominal pain episodes every 3 to 4 months. In the 3 months prior to her presentation, she reported three episodes of pancreatitis and one admission with lipase elevated to over 4000

IU/L (normal: 8-78). She was urged to take pancreatic enzymes with each meal.

At her consultation, she noted persistence of urgent diarrhea with undigested food at least once per day within 30 minutes of eating despite use of prescription-strength pancreatic enzyme support. She denied nausea, vomiting, bloating, cramping, and abdominal pain. She denied frequent, bothersome, or noticeable gas. She denied any trauma and any known exposures to potential toxins. She denied any predictability but noted that three episodes followed eating popcorn and three episodes followed eating different casseroles. She noted daily ice cream intake. Her medications included digestive enzymes, famotidine, lisinopril, and propranolol.

Her past medical history was remarkable only for heartburn/reflux symptoms since her teenage years, obstructive sleep apnea treated with CPAP, stage I hypertension, osteoarthritis, intermittent migraine headaches, and ductal carcinoma in situ. She underwent a bilateral mastectomy with reconstruction in 2008. Her family history was negative for any pancreatic or biliary disease.

On exam, she was calm and pain free. Her blood pressure was 112/78, pulse 54, and BMI 39.9 kg/m². Her physical exam was unremarkable. Her laboratory results were remarkable for: lipase slightly high at 66; albumin low at 3.6 with a normal total protein; vitamin D very low at 12 ng/mL (30-80) with a high normal PTH at 66 pg/mL (8.5-72.5); normal alpha-tocopherol and vitamin A levels and vitamin B₁₂ low normal at 373 pg/mL (200-1000) with high normal homocysteine at 13 umol/L (5-15.4).

DIAGNOSTIC FOCUS AND ASSESSMENT

The differential diagnosis for recurrent pancreatitis is well established (Table 1). Her evaluation demonstrated no structural or anatomic explanations as well as no classic metabolic and autoimmune etiologies. Although her workup had met or exceeded all pub-

Table 1 Known Causes of Recurrent Acute Pancreatitis

Alcohol
Autoimmune disease
Biliary calculus disease including microlithiasis
Biliary cystic disease
Congenital pancreatic anomalies
Cystic fibrosis
Duodenal obstruction
Hypercalcemia
Hypertriglyceridemia/hyperlipidemia
Infection
Medications
Neoplasm
Sphincter of Oddi dysfunction
Vasculitis

lished guidelines, she had no explanation and no plan for preventing future episodes. She reported living in fear of another pain crisis and hospitalization.

Therapeutic options are limited for patients with idiopathic recurrent acute pancreatitis but include cholecystectomy and endoscopic sphincterotomy, both of which this patient had undergone early in the time course of her illness (Table 2). To address an expanded differential diagnosis, she underwent specialized metabolomic and microbiome analysis that included stool DCA and LCA concentrations, pancreatic elastase concentration as well as a qualitative assessment of her intestinal ecology (CDSA 2.0, Genova Laboratories, Asheville, North Carolina).

Table 2 Timeline

1960s	Onset of intermittent heartburn, dyspepsia
2000:	Sharp epigastric pain episodes, cholecystectomy
2002:	Hip replacement
2002:	ERCP/sphincterotomy complicated by pancreatitis
2008:	Bilateral mastectomy with reconstructive surgery
2002-2009:	Multiple repeated episodes of idiopathic pancreatitis
2009:	Specialized stool testing, microbiome intervention
2011:	Repeat specialized stool testing
2009-2014:	No further episodes of pancreatitis

In April 2009, her secondary bile acids were measured as:

Lithocholic acid (LCA) normal at 3.35 (0.65-5.21 mg/g)
Deoxycholic acid (DCA) very high at >11.02 (0.67-6.76 mg/g).

Her culturable beneficial bacteria were surprisingly low. Ideal levels of all three are 4+ in concentration.

<i>E coli</i>	No growth
<i>Lactobacilli</i>	1+
<i>Bifidobacterium</i>	2+

The stool demonstrated heavy overgrowth of one gram-negative aerobe, *Pseudomonas aeruginosa*, at 4+ cultured growth with documented ciprofloxacin and ticarcillin sensitivity. Her stool demonstrated no *Clostridium difficile* by enzyme immunoassay. She demonstrated low normal pancreatic exocrine function with a pancreatic elastase of 287 ²g/g (>200).

THERAPEUTIC FOCUS AND ASSESSMENT

This stool analysis demonstrated three abnormal findings: (1) marked undergrowth of beneficial bacteria, (2) marked overgrowth of one potential aerobic pathogen, and (3) marked elevation of the toxic secondary bile acid, DCA. Normally, human stools should demonstrate no growth of *P aeruginosa* and should demonstrate high concentrations of *E coli*. The therapeutic plan was to replenish her vitamin status, clear the overgrowth with an antibiotic, and support the return of a balanced intestinal flora ecology through pre- and probiotic supplementation as well as restriction of animal fat intake.

Ciprofloxacin was prescribed at 250 mg by mouth twice a day for 10 days. A probiotic containing multiple species from the genus *Lactobacillus* and *Bifidobacterium* as well as the species of yeast termed *Saccharomyces boulardii* at 20 billion CFUs per capsule (Orthomolecular, Woodstock, Illinois) was administered once a day during the antibiotic and then doubled after the antibiotic was completed. The patient was urged to minimize ice cream intake and maximize vegetable intake, particularly prebiotic vegetables. She was encouraged to work with a holistic weight management program and engage in physical activity and other stress reduction techniques.

FOLLOW-UP AND OUTCOMES

After 48 months of follow-up, there have been no further episodes of pancreatitis. In September of 2011, repeat stool testing demonstrated normalization of the fecal DCA at 5.52 (0.67-6.76 mg/g) as well as the *E coli* concentration at 3+. The concentration of *Lactobacillus* species increased slightly to 2+ as did the pancreatic elastase to 444 ²g/g.

DISCUSSION

Initial evaluation fails to detect the cause of recurrent acute pancreatitis in 10% to 30% of patients or about 20,000 to 60,000 patients per year in the United States alone. In these patients, more extensive evaluations are warranted including ERCP and/or MRC.¹

Even then, as in this case, such evaluations may not provide an explanation in a large percentage of patients.² At this time, no published guidelines exist for further evaluation of idiopathic recurrent acute pancreatitis.

In this case report, the patient's recurrent acute pancreatitis appears related to markedly elevated levels

of the secondary bile acid termed DCA. Rebalancing the abnormal microbiome ecology appears responsible for resolving 7 years of recurrent acute pancreatitis. These observations have raised a new question: could recurrent acute pancreatitis result from elevated levels of DCA and microbiome imbalance?

Clinically, elevated levels of DCA are associated with increased risk of colon cancer^{3,4} as well as of cholesterol gallstone formation.^{5,6} However, until now, DCA has not been considered a potential etiologic agent for pancreatitis. This is despite the fact that scientists have, for many decades, infused three forms of DCA into experimental animals to induce reproducible pancreatic injury. The three forms include the bile salt sodium deoxycholate,⁷⁻⁹ the taurine conjugated bile salt (taurodeoxycholate),¹⁰ and the glycine conjugated bile acid (glycodeoxycholic acid).¹¹⁻¹³

To understand the potential role of the microbiome in pancreatitis requires a brief review of bile acids and their metabolism. The liver produces two primary bile acids to solubilize fats and fat-soluble nutrients, cholic acid (CA) and chenodeoxycholic acid (CDCA). These are conjugated to the amino acid glycine or taurine, which, at physiological pH, is almost fully ionized and considered a bile salt. These bile salts participate in an enterohepatic circulation. After release from the gallbladder, they travel from duodenum to jejunum to ileum where they are absorbed through a high affinity active transport and returned via the bloodstream to the liver.¹⁴

Approximately 5% of these salts pass on to the large intestine, where they undergo bacterially mediated 7 α -dehydroxylation to result in the potentially toxic secondary bile acids DCA and lithocholic acid (LCA). DCA can be passively reabsorbed through colonic mucosa and return to the liver. However, in the liver, it cannot be rehydroxylated to cholic acid and accumulates in the bile acid pool.¹⁵

The metabolic pathways necessary for secondary bile acid biotransformation are found in members of clostridial rRNA cluster XIVa which normally comprises just 0.0001% of all colonic flora. This cluster includes the anaerobic, gram positive, spore forming *Clostridium scindens*, *C. hiranonis*, *C. hylemonae*, and *C. scordellii*, as well as strains of *Blautia*, *Ruminococcaceae*, and *Lachnospiraceae* species.¹⁶

For the stool DCA to be high, these anaerobic bacteria must have been present in higher than usual concentrations. Of note, none of these could be reported by the aerobic culture techniques used in the testing. The antibiotic ciprofloxacin was appropriate for treatment of the *Pseudomonas aeruginosa* overgrowth but is not indicated for treatment of anaerobic bacteria. Reduction in the DCA-producing bacteria and in DCA itself could be attributed to random fluctuation or due to competitive exclusion by other bacterial species better able to compete in an environment changed by the ciprofloxacin, the probiotics, and the lifestyle changes.

This report builds upon a clear elimination of well-known causes of acute pancreatitis, complete cessation

of symptoms after treatment, documentation of DCA and microbiome normalization, and strong biological plausibility from the use of DCA to precipitate pancreatitis in animal models. Fecal DCA is easily tested. Needed now is a large observational study of fecal DCA levels in patients with recurrent acute pancreatitis.

PATIENT CONSENT

The patient provided written permission for publication of this case report.

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