

Probable association of acute pancreatitis with dicyclomine

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Dear Editor,

Acute pancreatitis (AP) is the leading gastrointestinal cause of hospitalization in the United States with approximately 275,000 discharges in 2012 (1). Gallstones and alcohol remain the most common causes of AP, accounting for 35%-40% and 30% of the cases, respectively (2, 3). Drug-induced pancreatitis (DIP) is a rare or uncommon cause of AP and accounts for 0.1%-2% of incidents (4).

A 55-year-old white female with a history of nonalcoholic steatohepatitis (NASH) presented to the ED complaining of 24-hour symptoms of nausea, vomiting, and severe epigastric pain radiating to the back. She did not have any change in her usual loose stool consistency with chronic lactulose use. Review of systems was otherwise unremarkable. Medical history was significant for obesity (body mass index, 30.6 kg/m²), Barrett's esophagus, and mixed hyperlipidemia. Surgical history included esophagogastroduodenoscopy and cholecystectomy (20 years ago). She denied any alcohol consumption. She had a 15 pack-year smoking history and admitted to occasional marijuana use; last use was few days before her admission. For several years, the patient had been taking aspirin, furosemide, spironolactone, lactulose, and sucralfate. She took lorazepam as needed for anxiety and codeine/acetaminophen occasionally for lower back pain exacerbations, and she took it after the severe abdominal pain started. The only new medication was dicyclomine, which was started about a month before her admission. Family history was unremarkable.

Physical examination was remarkable for an obese middle-aged female with stable vital signs, dry mucous membranes, and epigastric tenderness with no guarding or rigidity.

Laboratory results showed low platelets (154 K/uL), otherwise normal complete blood cell count, and nor-

mal basic metabolic panel and lipase (313 U/L) [13-60]. Non-fasting lipid panel showed mild elevation of cholesterol, triglyceride, and LDL.

Liver function tests, coagulation profile, ammonia level, calcium, magnesium, thyroid-stimulating hormone, IgG subclasses, and cardiac markers were within their normal reference values. Electrocardiogram was normal. Urine drug screen was positive for benzodiazepines, cannabis, and opioids.

Non-contrast computed tomography of the abdomen revealed absent gallbladder with a normal biliary ductal system, food-filled stomach, and normal liver, pancreas, and spleen. Abdominal ultrasound showed normal intrahepatic and extrahepatic biliary ductal system.

The patient was admitted to the hospital for supportive treatment. On the next day, her abdominal pain intensity improved, and fasting lipase dropped to 19 U/L. During hospitalization, her diuretics were held, diet was advanced as tolerated, analgesics were tapered, and her long-term medications were restarted. Dicyclomine was stopped, and she was discharged on most of her home medications along with statin and oral narcotics as needed, with no reported recurrent episodes during the 8-week period after discharge.

The patient presented with signs and symptoms of AP confirmed with an at least 3-fold increase of lipase levels. She did not drink alcohol, and she had a remote history of cholecystectomy with no evidence of biliary ductal system abnormalities on imaging studies. Autoimmune pancreatitis is unlikely with normal IgG subclasses. Although she had mild hypertriglyceridemia, level of <500 mg/dL is not a risk factor for AP. Despite chronic diarrhea owing to lactulose use, she did not have other symptoms to suggest celiac disease. NASH is not usually a risk factor for AP, neither the remainder of her medical problems, and it is unlikely for her AP to be attributed to her medical issues.

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Establishing the diagnosis of DIP is challenging due to its rare incidence, the variable latency among different drugs (first day of drug therapy to AP onset), and numerous other concurrent medications used prior to the onset (5). A high-index suspicion and thorough drug history to eliminate other potential causes are crucial in determining the diagnosis.

Although there are reports of codeine-induced pancreatitis (6), it is unlikely to be the trigger as she took it after her severe abdominal pain started. Smoking has recently emerged as an independent risk factor for AP, especially in non-gallstone pancreatitis (7,8). Both mild and severe cannabis-induced AP have been reported with variable latency (1-12 weeks) (5). Most of the reports have been in younger patients (age, <35 years), suggesting that AP after long-term cannabis use is uncommon (9).

This patient had been smoking tobacco and using marijuana for several years without prior pancreatitis. Even though the patient had been on several medications and substances, which could theoretically cause pancreatitis, dicyclomine was the most recent drug started. The temporal relationship makes dicyclomine more likely than the others as the culprit. Furthermore, the patient's symptoms improved after stopping dicyclomine, and she remained pain-free after she was restarted back on her other long-term medications. The patient was not considering re-challenge with dicyclomine with possible risk of pancreatitis recurrence.

Naranjo adverse drug reaction probability scale indicated that AP was a probable (score, 5) adverse drug reaction of dicyclomine (10). The common use of anticholinergic medications in variable GI diseases and procedures without higher risk for AP makes it difficult to establish an exact mechanism of the association. Dicyclomine is recommended to be used with caution in patients with hepatic impairment, and it is plausible that NASH and additional risk factor(s) might have some role in precipitating DIP after dicyclomine was initiated. Causality cannot be proven despite the suspected association as it is impossible to

exclude all other possible causes, including idiopathic AP. In conclusion, we present the first report of a probable association between dicyclomine and AP in a patient with NASH. Additional case series may shed more light on the nature of this relationship.

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Peer-review: Externally peer-reviewed.

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