A Case of Doxycycline-Induced Pancreatitis

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ABSTRACT

Introduction: Acute pancreatitis is a common cause of hospitalizations in the United States, causing approximately 230 000 to 275 000 annual admissions We present the case of a patient with acute pancreatitis likely due to doxycycline.

Case Presentation: A 64-year-old male was admitted after developing acute epigastric pain radiating to his back, a lipase of 6611 (units/L), and a computed tomography scan showing moderate peripancreatic inflammation. He had no recent alcohol use, his gallbladder was surgically absent, and he had no gallbladder pathology on evaluation; however, he had been started on doxycycline 10 days prior. While hospitalized, he was treated with pain medications, fluids, and antibiotics for aspiration pneumonia. His acute symptoms resolved, except for minor intermittent abdominal pain 2 months after discharge.

Discussion: Doxycycline-induced pancreatitis has been reported within 3 to 17 days of medication initiation. Given the temporal correlation and lack of other inciting etiologies, we determined the most likely etiology was doxycycline.

Conclusions: Further study is needed to understand the pathophysiology and incidence of doxycycline-induced pancreatitis.

INTRODUCTION

Acute pancreatitis is a common reason for hospitalizations in the United States, causing approximately 230 000 to 275 000 annual admissions.[1,2] Overall mortality estimates are between 5% and 30% in severe cases.[1,2] Alcohol use and gallstone disease are the most common causes, leading to 30%–35% and 30%–40% of cases, respectively.[1,2] Drug-induced pancreatitis (DIP) is likely an underreported and underrealized etiology of acute pancreatitis due to difficulty identifying and definitively proving a causal effect. Medications are estimated to cause between 0.1% and 2% of acute pancreatitis cases, but this is likely an underestimate as there are over 500 drugs reported to cause acute pancreatitis. Therefore, there is some concern that patients labeled with idiopathic pancreatitis may actually have DIP.[1-3]

The pancreas secretes inactive zymogens of digestive enzymes into the duodenum. The zymogens are activated by duodenal enterokinase cleaving trypsinogen into trypsin, which then activates the other pancreatic enzymes.[3] To prevent premature activation and autodigestion, the pancreas has several protective mechanisms.[3] These include trypsin inhibitor, which binds and reduces trypsin activity, autolysis of activated trypsin, and proteases, such as alpha-1-antitrypsin.[3] Acute pancreatitis occurs when these mechanisms are overwhelmed.[3]

Acute pancreatitis is the onset of pancreatic parenchymal and peripancreatic fat necrosis with inflammation. There are several systems used to characterize the severity of pancreatitis.[2] Regardless of classification, in mild pancreatitis, there is limited necrosis and/or organ failure. Comparatively, in severe pancreatitis, there is a considerable amount of pancreas necrosis. Comorbid intrapancreatic thrombosis, vascular disruption, intraparenchymal hemorrhage, and failure of one or more organ systems is present. It is believed that an inciting etiology, such as reflux by an obstructing gallstone, overwhelms the protective mechanisms leading to autodigestion of the pancreas causing an inflammatory response.[2,3]

Patients classically present with constant epigastric pain radiating to the back, with severity typically correlating to the severity of the pancreatitis.[2,3] Patients also may have associated jaundice,

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fevers, tachypnea, hypotension and/or hypoxia.[2,3] Grey Turner (flank ecchymosis) and Cullen (periumbilical ecchymosis) signs are often described in the literature; however, these are found only in approximately 3% of cases.[2,3] Complications can include pancreas necrosis, which can lead to late or recurrent infection. Pseudocysts – a walled off collection of fluid – can develop infections, hemorrhage, rupture, gastric outlet obstruction, splenic vein thrombosis/hemorrhage, and other complications.[2,3] Extrapancreatic manifestations affect numerous organ systems and can include cardiovascular (splanchnic vein thrombosis, pseudoaneurysm, worsening of chronic underlying coronary artery disease), abdominal (abdominal compartment syndrome), and pulmonary (worsening of underlying chronic lung disease). New severe complications are rare after 48 hours.[2,3]

Diagnosis of acute pancreatitis requires 2 of the following 3 findings: classic abdominal pain, lipase greater than 3 times the upper limit of normal, and characteristic imaging findings on appropriate imaging modalities (computed tomography [CT], magnetic resonance imaging [MRI], or ultrasonography).[3] DIP is harder to diagnose, as it involves ruling out common etiologies and performing an in-depth medication review and history.[2,3] Historical evaluation should consider prior episodes or other potential etiologies. Further evaluation with levels of liver enzymes, triglycerides, and calcium – as well as imaging evaluation with abdominal and endoscopic ultrasounds – should be completed. However, it is not recommended to perform endoscopic retrograde cholangiopancreatography (ERCP) if there is no evidence of choledocholithasis. If DIP is suspected, offending drugs should be discontinued or exchanged, if possible. A definitive diagnosis is difficult but is considered more likely if symptoms resolve with discontinuation of the drug of concern, especially if symptoms recur with medication challenge.[1-3]

Numerous classification systems have been defined over the years to determine the likelihood of a medication causing acute pancreatitis. One of the first systems reported was by Mallory and Kern, which defined the drug as a definite, probable, or possible cause of pancreatitis using the following criteria:[4]

1. Onset of pancreatitis had to occur while receiving treatment with the medication;
2. Disappearance of pancreatitis symptoms with discontinuation of the medication;
3. Exclusion of other causative etiologies; and
4. Symptom relapse with medication rechallenge.

Later classification systems by Trivedi and Pitchumoni revised stratifications to a 3-group system but concentrated on the frequency of cases and results of mediation rechallenge.[5] A third classification system has been proposed by Badalov et al, which focuses on the number of cases in the literature, whether there was a rechallenge, and the time between when the drug was initiated and pancreatitis occured.[6] The latency is classified as short (<24 hours), intermediate (1-30 days), or long (>30 days).[6] Badalov classifications are as follows:

- Class 1A: At least 1 case report with positive rechallenge, all other causes are excluded.
- Class 1B: At least 1 case report with positive rechallenge, other causes are not excluded.
- Class II: At least 4 cases in the literature, with at least 75% having consistent latency.
- Class III: At least 2 cases in the literature, no rechallenge, and no consistent latency.
- Class IV: Single case report without rechallenge, drug not fitting into other categories.[6]

Naranjo et al developed an Adverse Drug Reaction Probability scale to standardize evaluation of drug reactions (see Table 3).[7] The Naranjo scale and Badalov classification are similar; however, the Naranjo scale relies on more data points and is not designed specifically for DIP. The Naranjo scale relies on blood levels and placebo administration, while the Badalov classification relies heavily on case reports and the latency period. While the Naranjo scale initially was used for clinical research into drug-induced injury, it is not limited specifically to this purpose and is simple to utilize.[6,7]

Table 1. Past Medical History and Admission Lab Values

Past Medical History

- Severe peripheral artery disease with claudication
- Mesenteric ischemia
- Active smoker with 35 pack year history
- Coronary artery disease with prior myocardial infarction, status post 4 vessel coronary artery bypass
- Chronic pain syndrome with bilateral low back pain with sciatica
- Chronic obstructive pulmonary disease
- Stable angina
- Renal artery stenosis
- No history of pancreatitis
- Congestive heart failure with preserved ejection fraction
- Chronic kidney disease stage 3
- No history of alcohol abuse

Presenting Labs

- Complete blood cell count: WBC 15.9/uL, hemoglobin 15.5 g/dL, platelets 214/uL
- Electrolytes (in mmol/L): sodium 145, potassium 3.7, chloride 112, calcium 10.0
- Liver function tests: alkaline phosphatase 112 units/L, AST 13 units/L, ALT 21 units/L, total bilirubin 0.3 mg/dL
- Kidney function: BUN 27 mg/dL, creatinine 1.19 mg/dL, GFR 68 ml/min/1.73 m^2
- Other labs: carbon dioxide 23.0 mmol/L, albumin 3.3 g/dL, troponin 44 ng/L
- Cholesterol panel (in mg/dL): total 106, HDL 48, triglycerides 73, LDL 52

Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein

CASE PRESENTATION

A 64-year-old man presented to our outpatient primary care clinic for an elliptical excision of a skin lesion of the left buttock. There were no immediate complications; however, 8 days after the pro-

Table 2. Patients' Medications, Treatment Duration, Risk of Pancreatitis, Reported Number and Timeline of Development of Pancreatitis

Medications	Evidence Behind Potential Pancreatitis	Patient Duration of Therapy/Literature Reported Time Before Pancreatitis	Number of Reported Cases
Acetaminophen	Case reports, typically with overdose;[5] retrospective cohort study of overdose patients[11]	>17 years/up to 1 year after overdose	13 cases, 1 with reexposure;[5] 2958 cohort and 11 832 controls, HR 2.4 (95% CI, 1.29-4.47)[11]
Albuterol	No reported cases	6 years/NA	N/A
Amlodipine	Case reports FDA medication insert	6 years/time course not provided	<10 cases[5] Between 0.1% and 1%[13]
Aspirin	Case reports	6 years/time course not provided	<10 cases[5]
Atorvastatin	Reported cases; case control study FDA medication insert	6 years/hours to years; OR 1.67 (95% CI, 1.18-2.38) if used within 7 days, OR 1.15(95% CI, 0.87-1.52) if used >7 days ago[10]	2 cases;[12,14] 5810 cases w 5733 controls;[10] <10 cases[5] Frequency not reported[13]
Cistazole	No reported cases	6 years/NA	N/A
Clonidine	Reported cases from 1977; patients had other risk factors including cholestasis and thiazide treatment	6 years/NA	3 cases[15]
Doxycycline	Retrospective cohort study, case studies FDA Medwatch	10 days/2 – 28 days;[1,8,9] 1 case 273 days (chronic use for acne)[1]	4 patients reported across 3 case reports Frequency not defined[16]
Hydrocodone	No evidence for hydrocodone, population-based studies show increased risk of pancreatitis in people who undergo acetaminophen overdose FDA medication insert	>17 years/timeline not provided[5]	N/A[5] Frequency not specified, monitoring patients with known biliary dysfunction is recommended due to concern of sphincter of Oddi spasm[14]
Ibuprofen	Case reports FDA medication insert	>17 years/timeline not provided[5]	<10 cases[5] <1%[13]
Metoprolol succinate	No reported cases	5 years/NA	N/A
Morphine	Possible pancreatitis secondary to morphine overdose;[17] 1 case after routine dose;[18] cited literature for codeine and heroin[5] FDA medication insert	6 years/within 24 hours of initiation[5,17]	2 case reports,[17,18] opiate case reports numbered at 42 with 5 rechallenged[5] Frequency not specified, monitoring patients with known biliary dysfunction is recommended due to concern of sphincter of Oddi spasm[13]
Nitroglycerin	No reported cases	6 years/NA	N/A
Omeprazole	Case reports FDA medication insert	6 years/timeline not provided	<10 cases[5] <1%[13]
Paroxetine	No reported cases FDA medication insert	>17 years/timeline not provided[5]	N/A Frequency not defined[13]
Pregabalin	No reported cases	3 years/NA	N/A

Note: Data found by searching PubMed for "medication" and "pancreatitis" and reviewing results for each reported medication as well as reviewing the prescription drug insert for each medication for pancreatitis on AcessFDA.com.[13]

cedure, he was found to have a surgical site infection. Initially, he was prescribed cephalexin (Keflex) 500 mg 3 times a day, which he took for 4 days prior to transitioning to doxycycline 12 days after the procedure due to an upset stomach.

The patient was admitted to the hospital 22 days after the procedure (day 10 of doxycycline) with acute onset of epigastric pain radiating to the back, lipase of 6611 units/L, and a CT showing moderate peripancreatic inflammation consistent with pancreatitis. His history revealed he had not consumed alcohol recently, and his baseline alcohol consumption was 1 to 2 drinks every other month. He took ibuprofen 800 mg intermittently; the last dose was within 1 week of admission. Doxycycline was last taken the afternoon prior to admission. He was diagnosed with pancreatitis and admitted.

On admission, omeprazole was changed to pantoprazole per hospital formulary. CT abdomen revealed moderate peripancreatic inflammation consistent with pancreatitis, multiple nonobstructive bilateral renal calculi with underlying moderate-

to-severe left renal atrophy, and mild sigmoid diverticulosis. Right upper quadrant abdominal ultrasound showed that the patient's gallbladder was surgically absent, his liver was normal in architecture with no biliary ductal dilation, and the common bile duct was unremarkable with a maximal width of 4 mm. The pancreas was poorly visualized due to overlying bowel gas, and his right kidney was unremarkable. Chest x-ray revealed chronic cardiomegaly with minimal congestion. Past medical history and admission labs are noted in Table 1; medications, duration of therapy, and potential for acute pancreatitis are noted in Table 2.

Table 3. Patient's Calculated Naranjo Score[7]

Question	Yes	No	Don't Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	-1
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total Score				4

Total scores range from -4 to +13. Reactions are considered doubtful if below 0, possible if between 1 and 4, probable if between 5 and 8, and definite if 9 or above. Scores for individual questions are calculated based on specific criteria for each question. See Naranjo et al for specific criteria.[7]

During his hospital course, the patient was allowed nothing by mouth and was treated with intravenous opioids and aggressive fluid resuscitation. His pain improved and he started a clear liquid diet on day 3 of hospitalization; aspirin and ibuprofen were discontinued. On hospital day 4, he was noted to have worsening dyspnea and increasing oxygen requirement. A chest x-ray showed a new right lower lobe infiltrate compared to his admission x-ray, and his white blood cell (WBC) count had increased to 17 400/uL. He was started on cefepime 1g twice daily and vancomycin dosed per pharmacy for aspiration pneumonia. Echocardiogram showed an ejection fraction above 55% and diastolic function with an A wave greater than the E wave. On day 5, supplemental oxygen needs decreased. On day 6, the patient started a fat-restricted diet and was given metronidazole 500 mg 3 times daily due to a persistently elevated WBC count and concern for abdominal infection. Repeat abdominal CT scan to evaluate for infection on day 7 showed mild pancreatitis, which was felt to be improving compared to admission CT. He experienced improvement on antibiotics and on a fat-restricted diet during the hospitalization.

On hospital day 9, the patient was discharged on cefdinir 600 mg daily for 7 days for hospital-acquired aspiration pneumonia. On follow-up about 8 weeks after discharge, his primary care clinician indicated he had weaned off his chronic opioids and had some mild, intermittent residual abdominal pain. A lipase checked at this time was normal. Unfortunately, the patient passed away from an acute myocardial infarction about 16 weeks after admission.

DISCUSSION

Doxycycline-induced pancreatitis is a seemingly rare, but previously documented event. Chadalavada et al performed a retrospective cohort study looking at 841 cases of acute pancreatitis and found 31 cases secondary to medications, including doxycycline.[1] Additionally, there are several reported probable cases of pancreatitis as a result of doxycycline treatment.[1,8,9]

In our case, more common etiologies, such as trauma, ethyl alcohol, hypertriglyceridemia, post ERCP, gallstone disease, and genetic disorders were ruled out via the patient's history. Evaluation for autoimmune and malignant etiologies of his pancreatitis was not pursued due to the lack of typical symptoms (eg, weight loss, jaundice, or pancreatic enlargement), and his clinical improvement. Similarly, viral infections were thought to be unlikely without a history of corresponding symptoms.

There was a possibility that the pancreatitis was related to longstanding vascular disease, aspirin, omeprazole, amlodipine, or atorvastatin. However, this was thought to be unlikely due to the temporal correlation of doxycycline treatment. The patient's only medication documented to cause pancreatitis after long-term use was atorvastatin, possibly through interactions with the CYP3A subsystem.[19] However, this appears to be a weak correlation, with an odds ratio of 1.67 (95% CI, 1.18-2.38).[10] Rather than directly causing pancreatitis, it is possible that atorvostatin decreases the threshold for pancreatitis, as it has been noted that DIP is more likely in patients with multiple comorbidities and polypharmacy.[11,19] This is certainly a possibility for our patient given his comorbidities and polypharmacy.

As in most idiopathic versus DIP cases, it would be difficult to definitively prove doxycycline as the cause without rechallenging, which has obvious ethical concerns. The patient's Naranjo score was calculated at 4, indicating a possible reaction (see Table 3).

Furthermore, the time course is within the timeframe of 3 to 15 days reported in several other studies.[1,8,9] Not all authors calculated a Naranjo score, so it is more difficult to quantify the likelihood of reaction.[1,8,9] We would argue that quantification should be recommended in all suspected cases, due to the difficulty identifying and subsequently diagnosing DIP. Therefore, we argue that with the addition of our case, the Badalov classification for doxycycline would increase to level II within the available literature.[6]

CONCLUSIONS

DIP is a rare etiology of acute pancreatitis, and doxycycline is a medication with case reports supporting it as an inciting etiology. Increasing knowledge of medications with the potential to cause acute pancreatitis will help with diagnostic clarity and therefore elucidate the true incidence and prevalence of drug-induced pancreatitis.

We present another case of possible doxycycline-induced pancreatitis to educate clinicians and add to the body of evidence of medications that can cause pancreatitis. Our intent is to increase clinicians' recognition of potential DIP and facilitate further investigation into the topic.

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