Probable doxycycline-induced acute pancreatitis

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Purpose. A probable case of doxycycline-induced pancreatitis is reported.

Summary. A 51-year-old man was admitted to the emergency department with a one-week history of extreme fatigue, malaise, and confusion. Three days earlier he had been started on empirical doxycycline therapy for presumed Lyme disease; he was taking no other medications at the time of admission. A physical examination was remarkable for abdominal tenderness. Relevant laboratory data included a lipase concentration of 5410 units/L (normal range, 13–60 units/L), an amylase concentration of 1304 (normal range, 28–100 units/L), and a glycosylated hemoglobin concentration of 15.2% (normal, <5.7%). Tests for immunoglobulin G4, Lyme disease antibodies, influenza strains, human immunodeficiency virus, and hepatitis A, B, and C were all negative. Blood, urine, cerebrospinal fluid, and respiratory cultures showed no growth. Abdominal computed tomography findings were consistent with acute pancreatitis (AP). The patient was admitted to the intensive care unit and intubated, and doxycycline was discontinued. With vasopressor support, aggressive fluid resuscitation, hemodialysis, and an insulin infusion, the patient's clinical course rapidly improved over five days. Scoring of the case via the method of Naranjo et al. yielded a score of 6, indicating a probable adverse reaction to doxycycline.

Conclusion. A man developed AP three days after starting therapy with oral doxycycline, and the association between drug and reaction was determined to be probable. His case appears to be the third of doxycycline-associated AP, although tigecycline, tetracycline, and minocycline have also been implicated as causes of AP.

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Drug use is a relatively uncommon cause of pancreatitis, accounting for only about 2% of cases of acute pancreatitis (AP) in the general population.[1] The diagnosis of drug-induced pancreatitis depends on the demonstration of a temporal sequence from administration to development of AP, exclusion of other causes, and a positive rechallenge with the drug. A review of the literature revealed two reports of doxycycline-induced pancreatitis.[2,3] Here we present what we believe to be the third published case report of doxycycline-induced pancreatitis.

Case report

A 51-year-old man presented with a one-week history of extreme fatigue, malaise, and confusion. Three days prior to hospital admission, he was empirically started on oral doxycycline for presumed Lyme disease. His past medical history included dyslipidemia controlled with lifestyle changes. He had no significant surgical or family history and did not smoke, consume alcohol, or use illicit drugs. His only medication at the time of admission was doxycycline 100 mg orally twice daily. On admission, the patient had a Glasgow Coma Scale score of 6, a mean arterial pressure of 50 mm Hg, a heart rate of 102 beats/min, a respiratory rate of 27 breaths/min, and a temperature of 95.4 °F. A physical examina-

tion was remarkable for abdominal tenderness, but no rash or lymphadenopathy was noted.

Relevant laboratory data included a serum sodium concentration of 153 meq/L (normal, 136–145 meq/L), a serum potassium concentration of 4.1 meq/L (normal, 3.4–5.3 meq/L), a serum bicarbonate concentration of 15 meq/L (normal, 22–33 meq/L), a blood urea nitrogen concentration of 80 mg/dL (normal, 8–21 mg/dL), a serum creatinine concentration of 4.6 mg/dL (normal, 0.5–1.3 mg/dL), a serum glucose concentration of 1,161 mg/dL (normal, 65–91 mg/dL), serum osmolality of 420 mOsm/kg (normal, 285–295 mOsm/kg), a white blood cell count of 24,800 cells/mm^3 (normal, 4,000–11,000 cells/mm^3), a hematocrit of 42.8% (normal, 39–54%), a serum ionized calcium concentration of 1.09 mmol/L (normal, 1.17–1.33 mmol/L), a serum aspartate transaminase concentration of 77 units/L (normal, 10–55 units/L), a serum alanine transaminase concentration of 60 units/L (normal, 10–55 units/L), a serum total bilirubin concentration of 0.6 mg/dL (normal, 0.2–1 mg/dL), a serum lipase concentration of 5,410 units/L (normal, 13–60 units/L), a serum amylase concentration of 1,304 units/L (normal, 28–100 units/L), a serum triglyceride concentration of 118 mg/dL (normal, <150 mg/dL), and a glycosylated hemoglobin concentration of 15.2% (normal, <5.7%). The arterial pH was 7.12, the arterial partial pressure of oxygen was 111 mm Hg, and the alveolar partial pressure of oxygen was 330 mm Hg.

Tests for immunoglobulin G4; Lyme disease antibodies (immunoglobulins G and M); influenza A and B; hepatitis A, B, and C; and human immunodeficiency virus were negative. Blood, urine, cerebrospinal fluid, and respiratory cultures showed no growth.

The results of right upper quadrant ultrasound and a chest x-ray were normal. A computed tomography (CT) scan of the abdomen

KEY POINTS

- Doxycycline-induced pancreatitis is a rare cause of acute pancreatitis and has no clinical features that distinguish it from other causes of pancreatitis.

- Healthcare providers should be aware of the causal relationship and clinical course of doxycycline-induced pancreatitis, act judiciously in excluding other causes of acute pancreatitis, and discontinue the drug if there is a high clinical suspicion.

- The adverse drug reaction probability scale of Naranjo et al. can guide a practitioner in estimating the probability of an adverse drug reaction.

showed mild stranding in the surrounding fat near the head of the pancreas, wall thickening of the

duodenum, and no encapsulated fluid collection (Figure 1). On presentation, the patient's Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 21. The patient was admitted to the intensive care unit (ICU), intubated, and started on vasopressor support; he received aggressive fluid resuscitation. Doxycycline was discontinued. Hemodialysis and an insulin infusion were initiated. Once resuscitative efforts had begun, the patient's metabolic abnormalities were corrected and his clinical course rapidly improved. On day 5 of his ICU stay, the patient was weaned off of ventilator and vasopressor support, with signs of resolution of multiorgan failure noted. Due to ethical reasons, a rechallenge with doxycycline was not performed.

Discussion

The diagnosis of AP is based on clinical signs and symptoms, laboratory data, and radiographic imaging. The classic clinical features of pan-

Figure 1. Abdominal computed tomography scan showing fat stranding (arrow), a feature consistent with acute pancreatitis.

Table 1. Case Reports of Pancreatitis Associated With Tetracycline Derivatives[a]

Ref.	Age (yr) and Sex	Comments on Risk Factors	Nontetracycline Medications	Tetracycline Derivative and Regimen	Onset of Symptoms (days)[b]	Days to Recovery From Symptoms[c]	Peak Serum Amylase and Lipase Values (units/L)[d]	Days to Normalization of Serum Amylase and Lipase Values
2	21, M	No alcohol use, hypertriglyceridemia, or gallbladder disease	Citalopram	Doxycycline (regimen NR)	10	21	NR	21
3	33, F	No alcohol use, cholelithiasis, or trauma	Ornidazole	Doxycycline 500 mg orally twice daily	3	2	Amylase, 220; lipase, 595	3
4	69, F	No alcohol or illicit drug use	Acetaminophen, aspirin, clindamycin, famotidine, gabapentin, meropenem, metoprolol, mirtazapine, tramadol, vancomycin zolpidem	Tigecycline 50 mg i.v. twice daily	7	5	Amylase, 926; lipase, 749	5
7	35, M	No cholelithiasis, hypertriglyceridemia, or hypercalcemia	None	Tigecycline 50 mg i.v. twice daily	13	2	Amylase, NR; lipase, 1000	43
8	64, F	No alcohol use	Hydromorphone, levothyroxine, pantoprazole	Tigecycline 50 mg i.v. twice daily	14	3	Amylase, 806; lipase, 406	5
9	55, F	NR	Fluconazole, levofloxacin, linezolid, nystatin, vancomycin	Tigecycline (regimen NR)	10	2	Amylase, 180; lipase, 160	7
10	NR, M	No alcohol use, cholelithiasis, total parenteral nutrition, ERCP, trauma, hypertriglyceridemia, or hypercalcemia	Amikacin, propofol	Tigecycline 100 mg orally daily	7	10	Amylase, 312; lipase, 382	10

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11	17, M	No alcohol use or trauma	None	Tetracycline hydrochloride 500 mg orally four times daily	2 yr	21	Amylase, 375; lipase, 58	NR
11	14, M	Cystic fibrosis but no abdominal trauma, previous pancreatitis, illicit drug use, or cholelithiasis	Pancreatic enzymes	Tetracycline hydrochloride 250 mg orally four times daily	18	28	Amylase, 1518; lipase, NR	28
12	21, NR	No alcohol use or abdominal trauma	None	Tetracycline 250 mg orally four times daily	5	21	Amylase, 1125; lipase, 7.5	21
13	29, F	Cystic fibrosis but no alcohol or corticosteroid use or gallstones	Fluoxetine, fluticasone, levothyroxine, theophylline	Minocycline 100 mg orally twice daily	10	3	Amylase, 486; lipase, 252	3
13	21, F	NR	None	Minocycline 100 mg orally twice daily	7	7	Amylase, 1013; lipase, 902	4
Current case	51, M	No alcohol use, hypertriglyceridemia, hypercalcemia, trauma, ERCP, bacterial infection, or cholelithiasis	None	Doxycycline 100 mg orally twice daily	3	5	Amylase, 1305; lipase, 5485	5

[a]NR = not reported, ERCP = endoscopic retrograde cholangiopancreatography.
[b]After initiation of tetracycline derivative.
[c]After discontinuation of tetracycline derivative.
[d]Normal ranges: amylase, 28–100 units/L; lipase, 13–60 units/L.

creatitis are abdominal pain, nausea, and vomiting. Confirmatory laboratory data often show elevated serum amylase and lipase concentrations. Radiographic findings can show an edematous pancreas, with fat stranding on CT. Our patient had all three of these findings at presentation, prompting the diagnosis of AP. The two most common causes of AP are biliary tract disease (40% of cases) and alcohol use (35% of cases).[4] AP may occur after endoscopic retrograde cholangiopancreatography or as a result of trauma, infection, hypercalcemia, hypertriglyceridemia, tumors, or autoimmune disease; it may also be idiopathic in etiology.[4,5]

Acute bacterial infection was ruled out in our patient due to a normal urinalysis, a normal chest x-ray, four sterile blood cultures, and sterile cerebrospinal fluid. Although the patient's primary care physician had made a presumptive diagnosis of Lyme disease, there was no reported history of tick bites or high-risk behaviors predisposing to Lyme disease, and the initial physical examination did not find any objective signs of Lyme disease. The workup for Lyme disease antibodies was negative. A literature review found no evidence of any association between Lyme disease and AP.

Drug-induced pancreatitis is a diagnosis of exclusion; other etiologies of pancreatitis should be ruled out before concluding that drugs are the cause.[1] Using the probability scale of Naranjo et al.,[6] we assigned a score of 6 to the case described here (2 points for the reaction occurring after administration of doxycycline, 1 point for the reaction improving after removal of doxycycline, 2 points for exclusion of alternative causes, and 1 point for a previous report in the literature), indicating a probable adverse reaction to doxycycline. In general, drug-induced pancreatitis has been discussed in case reports demonstrating the temporal relationship between drug intake and the onset of pancreatitis, confirmation via re-

exposure, and the absence of other precipitating factors.[1]

After performing a literature search using keywords including *tetracycline* and *pancreatitis*, two cases of doxycycline-, five cases of tigecycline-, three cases of tetracycline-, and two cases of minocycline-induced pancreatitis were found (Table 1).[2-4,7-13] In these cases, the mean age of patients with pancreatitis associated with a tetracycline was 34 years (range, 14–69 years), with nearly equal numbers of male and female patients. All patients reported nausea and abdominal pain after initiation of a tetracycline. The onset of AP after drug intake ranged from 3 days to 2 years, but most drug-induced pancreatic injury occurred within 14 days after initiation of tetracycline use. Recovery from clinical symptoms occurred in 2–28 days, and it took 3–43 days for amylase and lipase values to normalize after cessation of the drug. These cases help to identify the average time to recovery from pancreatitis after tetracycline exposure.

Several systems that provide reliable prognostic indicators for patients with AP have been created and validated. The APACHE II scoring system can be applied within hours after admission, and direct associations of APACHE II scores with ICU death rates have been demonstrated.[14] The components of the APACHE II scoring system take into account temperature; mean arterial blood pressure; heart and respiratory rates; alveolar-arterial oxygen pressure; partial pressure of oxygen in arterial blood; arterial pH; serum bicarbonate, sodium, potassium, and creatinine concentrations; the hematocrit value; and the white blood cell count.

Here we present a case involving newly diagnosed diabetes mellitus in a patient with a hyperosmolar hyperglycemic state and severe AP three days after initiation of doxycycline therapy. The patient's prodrome of general malaise and altered mental status was thought to be a result of his hyperosmolar hyperglyce-

mic state (as evidenced by a serum glucose concentration of 1161 mg/dL and a serum osmolality of 420 mOsm/kg). Rapid correction of the patient's metabolic abnormalities resulted in improvement in his clinical condition. Shortly after his arrival in the emergency department, our patient had an APACHE II score of 21, correlating with a 40% risk of death.[14] Other possible etiologic factors, including alcohol use, gallstones, hypercalcemia, hyperlipidemia, infection, and autoimmune causes, were ruled out via history taking, blood chemistry assays, microbiology studies, and radiodiagnostic imaging. As noted above, scoring of the case using the probability scale of Naranjo et al. yielded a score of 6, indicating a probable adverse drug reaction caused by doxycycline.[6] After eliminating other common causes of AP, we concluded that our patient probably developed pancreatitis induced by doxycycline. Identifying doxycycline as a possible cause of AP, properly ruling out other causes of AP, and avoiding further use of the antibiotic led to full resolution of the patient's symptoms. Healthcare providers should be aware of the causal relationship between doxycycline and AP in otherwise unexplained AP and act judiciously in discontinuing the drug.

Conclusion

A man developed AP three days after starting therapy with oral doxycycline, and the association between drug and reaction was determined to be probable. His case appears to be the third of doxycycline-associated AP, although tigecycline, tetracycline, and minocycline have also been implicated as causes of AP.

Disclosures

The authors have declared no potential conflicts of interest.

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