Case Report

Drug-Induced Pancreatitis: A Rare Manifestation of Doxycycline Administration

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Abstract

Context: Drug-induced pancreatitis (DIP) is rare, but as there are no systematic data on it, the true incidence is not known. Although numerous and varied drugs have been associated with DIP, the clinical evidence on doxycycline-induced pancreatitis is sparse. **Case Report:** We present the case of a 58-year-old female who presented with complaints of nausea and severe epigastric pain. Her medications included doxycycline which she had been on for only 2 days. Computed tomography of her abdomen showed mild enlargement of body of the pancreas with peripancreatic fatty infiltration, along with lipase level suggestive of acute pancreatitis. In the absence of classical risk factors for acute pancreatitis, a diagnosis of DIP secondary to doxycycline therapy was made. Immediate withdrawal of the drug was accompanied by relief of symptoms and resolution of pancreatitis. **Conclusion:** This report implicates doxycycline as an etiological factor for acute pancreatitis. Knowledge regarding doxycycline related pancreatitis is of paramount importance in order to diagnose cases early and institute effective treatment in patients who are undergoing therapy with this drug.

Keywords: Acute pancreatitis, doxycycline, drug-induced pancreatitis (DIP)

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Introduction

Acute pancreatitis is a life-threatening condition affecting around 45 per 100,000 people annually.[1] Drug-induced pancreatitis (DIP) is a rare variant of acute pancreatitis. The true incidence of DIP is not known and evidence has mainly been derived from case reports and case series. Doxycycline administration, albeit rare, may result in DIP. The literature is scant on the association of DIP with doxycycline.[2-4] We present this unusual case in which DIP symptoms were demonstrated following the second day of initiation of doxycycline treatment. In our patient, diagnosis of DIP was made by exclusion of all common etiologies of acute pancreatitis such as alcohol, gallstones, hypercalcemia, hypertriglyceridemia, infection, trauma, or medical procedures such as endoscopic retrograde cholangiopancreatography (ERCP). After confirmation, the patient was treated with discontinuation of doxycycline and in addition, conservative treatment was instituted. The patient had an uneventful recovery and has been symptom-free for over 1 month.

Case Presentation

A 58-year-old African-American female presented to the Emergency Department (ED) of Mount Sinai St. Luke's and Roosevelt Hospital Center with mild nausea

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and severe epigastric pain. Her past medical history was significant for hypertension, noninsulin-dependent diabetes mellitus, and osteoporosis with recent ankle and tibial bone fracture, which was managed with orthopedic procedures (Ilizarov ankle arthrodesis and fixation of tibia). On orthopedic outpatient follow-up, she was found to have internal pin (orthopedic hardware) site infection. She was prescribed doxycycline (Monodox®, Par Pharmaceuticals Inc., Spring Valley, New York, USA) 200 mg twice a day per oral, in anticipation of repeat irrigation of the infected site. On the second day of initiation of doxycycline, the patient started feeling nauseous with epigastric pain, and came to visit the ED. The pain was rated as severe, gnawing in nature, and was radiating to the back. She was nonalcoholic, non-smoker, and drug-free.

The patient was hemodynamically stable. Physical examination revealed epigastric and right upper quadrant tenderness with hypoactive bowel sounds. Rebound tenderness and abdominal wall rigidity were absent. Laboratory evaluation was remarkable for serum lipase 2,508 IU/L (normal, 23-300) and C-reactive protein 5.8 mg/dL (normal, 0-1). Urinalysis was negative for acute infection and urine human chorionic gonadotrophin was negative for pregnancy. Liver function tests and lipid panel were within normal limits.

Ultrasound of the right upper quadrant demonstrated mild proximal dilatation of common bile duct with smooth tapering of the duct distally, which were usual findings as our patient had undergone cholecystectomy. No common bile duct stone was seen [Figure 1]. Computed tomography scan demonstrated mild enlargement of the body of the pancreas [Figure 2]. Peripancreatic fatty infiltration was evident and surgical clips were noted in the gallbladder fossa [Figure 3]. Necrosis or peripancreatic fluid collection was absent. Four months earlier, the patient had a normal-appearing pancreas and peripancreatic fat [Figure 4]. After ruling out common etiologies of acute pancreatitis, drug-induced pancreatitis (DIP) was diagnosed. On review of the literature for all possible drugs responsible for DIP, we concluded that our patient had doxycycline-induced pancreatitis.

Subsequently, doxycycline was discontinued. The patient was initiated on intravenous (IV) hydration, antiemetics, and morphine. IV vancomycin was administered for internal pin site infection. On the third day of hospital admission, the pain and nausea improved. After symptomatic improvement, she underwent an uneventful orthopedic procedure for washout of the infection site, and was discharged from the hospital after providing supportive care. One month follow-up visit revealed complete recovery of the symptoms.

Discussion

DIP has an estimated incidence of 0.1-5.3% in the human immunodeficiency virus (HIV) negative population.[5,6] A retrospective study concluded in 1993 in Germany demonstrated that 22 out of 1,613 (1.4%) cases of acute pancreatitis were related to drugs.[7] A recent report of 170 cases of acute pancreatitis from the Czech Republic demonstrated that 5.3% cases were of DIP.[6] Another study attributed an incidence of DIP to be 4.8% of all acute pancreatitis cases.[8] However, the exact incidence of DIP is difficult to determine owing to the rare presentation, and blind labeling of pancreatitis as idiopathic. It warrants larger, case-controlled studies to determine the incidence and prevalence of DIP.

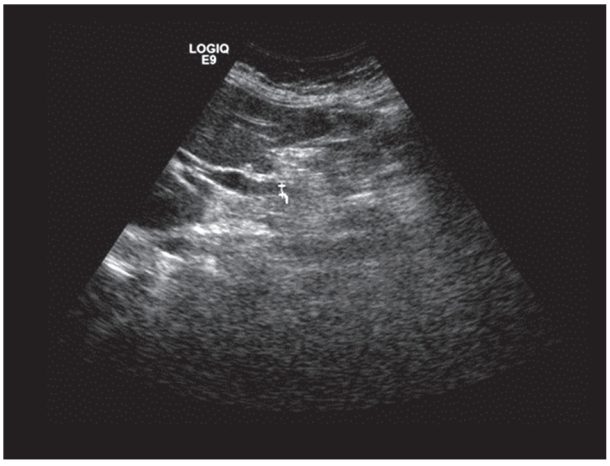

Figure 1: Right upper quadrant ultrasound demonstrating mild proximal dilatation of the common bile duct with smooth tapering of the duct distally. No common bile duct stone is present

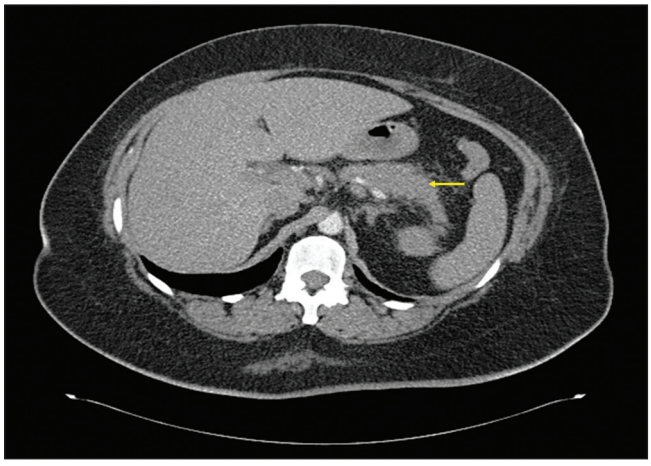

Figure 2: Contrast-enhanced computed tomography at the level of pancreas. Arrow demonstrates mild enlargement of the body of the pancreas

DIP poses a diagnostic challenge to clinicians, as it has no specific clinical characteristics distinguishing it from other forms of acute pancreatitis. Biliary disease (38%) and alcoholism (36%) are the most common etiologies of acute pancreatitis.[9] In our case, imaging studies ruled out biliary disease and the patient had no history of alcohol abuse, with normal serum triglyceride. Although she had trauma and had undergone a recent surgery, the timing of onset of the symptoms was more consistent with doxycycline-induced disease.

According to the World Health Organization (WHO), over 525 different drugs were implicated in the etiology of DIP between 1968 and 1993.[10] Afterward, addition of new drugs to the list has been made, including numerous antibiotic medications. Tetracycline has long been designated as a causative agent in acute pancreatitis. However, there are only four reports of DIP following doxycycline, either as a monotherapy or in combination therapy, shown in Table 1.[2-4] To our surprise, all four were female patients. However, reports of doxycycline as the sole etiology of DIP, as in our case, are extremely rare. DIP manifests variable time of onset. Previously, antibiotic-associated pancreatitis has been reported after 1 month to almost immediately after the administration of drugs.[11-13]

We believe our case is unique in terms of doxycycline as the sole etiology of DIP and symptoms of DIP developed 2 days after doxycycline therapy, which is the shortest reported time for doxycycline-induced pancreatitis.

Doxycycline is a well-studied and the Food and Drug Administration (FDA) approved tetracycline derivative antibiotic. It has well-supported clinical benefits in multidisciplinary practices. Doxycycline has been effectively used to treat a wide variety of bacterial infections, acne vulgaris, and periodontitis. However, doxycycline-induced pancreatitis is a rare but devastating condition and prompts the need of an early diagnosis. The exact pathophysiology for this phenomenon remains a mystery and can only be hypothesized on. In one large study conducted in the Netherlands involving 55 cases of DIP between 1977 and 1998, doxycycline was proposed to have a probable causal relationship in the development of acute pancreatitis.[14] Due to rarity of the condition, we may attribute DIP in our patient as an idiosyncratic drug reaction to doxycycline. The incidence and prevalence of idiopathic pancreatitis has been rapidly growing. Therefore, it is imperative to consider and study doxycycline and other drugs as possible culprits of acute pancreatitis.

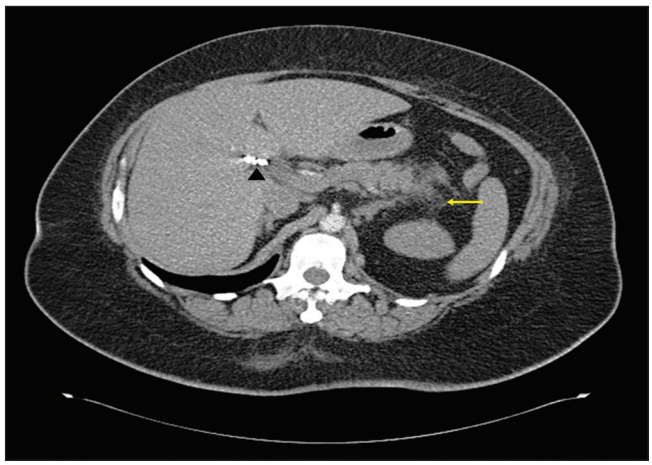

Figure 3: Contrast-enhanced computed tomography at the level of pancreas. Arrow in yellow color demonstrates peripancreatic fatty infiltration. Black arrowhead showed surgical clips in the gallbladder fossa indicating the patient's status after cholecystectomy

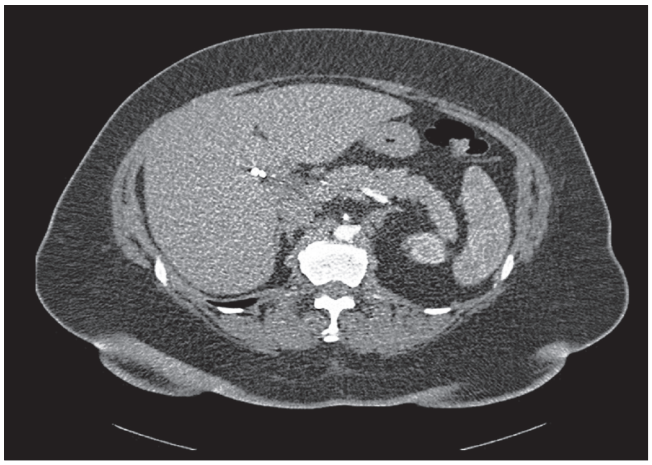

Figure 4: Contrast-enhanced computed tomography at the level of the pancreas performed 4 months prior to the current presentation. Normal-appearing pancreas and peripancreatic fat were demonstrated

Table 1: Data of the doxycycline-induced pancreatitis patients

Authors	Age	Gender	Alcohol	Lipids level	Dose of doxycyline	Pancreatitis development time	Stage of balthazar in CT	Ref. No.
Ocal *et al*.*	33	Female	None	Normal	1,000 mg/day	3 day	Normal	2
Achecar Justo L *et al*.†	75	Female	None	Normal	400 mg/day	14 days	Severe	3
Wachira *et al*.	21	Female	None	Normal	NA	15 days	Mild	4
Inayat F *et al*.	58	Female	None	Normal	400 mg/day	2 day	Mild	Current

*Doxycycline in combination therapy with ornidazole, †Doxycycline in combination therapy with amikacin and rifampicin, CT = Computed tomography, Ref = Reference

In conclusion, we report this rare complication of doxycycline manifested in the form of DIP. A high index of suspicion for DIP should be maintained. Physicians should consider checking serum amylase and lipase levels for patients presenting with gastrointestinal symptoms, even as early as after a few days of doxycycline administration. Furthermore, new epidemiological studies are warranted to investigate this unusual association.

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Conflicts of interest

There are no conflicts of interest.

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