METRONIDAZOLE INDUCED ACUTE PANCREATITIS: A CASE REPORT AND REVIEW OF LITERATURE

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Summary

Metronidazole is a known but uncommon cause of acute pancreatitis. The reported cases were mild to moderate in severity with moderate enzyme elevation. Only two cases so far had diagnostic imaging confirming the presence of pancreatic inflammation. In all the eight cases reported, the discontinuation of metronidazole resulted in rapid recovery both clinically and enzymatically. Interestingly all reported cases are females. Although uncommon, metronidazole use should be considered as a potential precipitant in patients presenting with acute pancreatitis.

Key words: Metronidazole, Pancreatitis, Adverse effect, Case report

Introduction

Metronidazole is very uncommon, but recognized, etiology of acute pancreatitis. Reports indicate that this adverse effect can happen under different circumstances. The pathogenesis is believed to be mediated through direct effect of the drug through 1) its penetration into pancreatic tissue, 2) the toxic effect of free radicals on B cells and 3) immunologic damage to pancreatic ducts. [1]

Case Report

A 62-year-old Hispanic female was evaluated in the emergency department for constant epigastric pain for three days. The patient had experienced up to ten loose, brown stools per day for three weeks prior to her presentation. Nine days prior to admission, her primary physician

empirically prescribed a ten day course of metronidazole. Her diarrhea subsequently resolved, but on the fifth day of metronidazole therapy she developed abdominal pain. At the time of her presentation, she described the pain as severe, constant and non-radiating epigastric pain, which was aggravated by deep inspiration and movement and was not related to eating, however lying on her left side brought minimal relief. Pain was associated with nausea, but not vomiting. Additional symptoms included mild dizziness and chills, but no fever. The patient denied any prior similar episodes.

In the emergency department, she was noted to be in moderate distress. The patient was afebrile, bowel sounds were present and there was marked epigastric tenderness. The initial laboratory tests revealed elevated Lipase (877 U/L), Amylase (384 U/L), CRP (9.19 mg/dl) and normal leukocyte count. Her chemistry and liver panel were normal with a total bilirubin of 0.7 mg/dl. Stool culture for bacterial pathogens, and stool for ova and parasites was negative. *Clostridium difficile* antigen testing was negative. Lipid panel showed no elevation of any components. Urine analysis was remarkable for cloudy urine, trace glucose, albumin, leukocyte esterase, and 11-25 WBC / HPF but she denied urinary symptoms. Serial cardiac enzymes were normal and an EKG did not show any changes consistent with an ischemic event. A CT scan was performed and was remarkable for the presence of acute pancreatic inflammation without evidence of necrosis. Right upper quadrant ultrasound confirmed her post cholecystectomy status and revealed no evidence of biliary obstruction or choledocholithiasis.

Common bile duct diameter was unremarkable. Metronidazole was the patient's only medication previously documented to induce acute pancreatitis. Metronidazole was discontinued on admission. The patient denied ever using alcohol and had quit smoking about 4 years ago. There was no family history of pancreatitis or cystic fibrosis. The patient demonstrated a rapid recovery after discontinuation of the metronidazole and with supportive care. Her lipase level decreased markedly and amylase returned to normal over 48 hours. After recovery and resumption of normal diet, she once again developed diarrhea. The diarrhea was symptomatically controlled by a single dose of loperamide and the next day EGD and colonoscopy were performed. EGD revealed multiple small non-penetrating gastric ulcers. Testing for *Helicobacter pylori* was negative, and biopsies showed no evidence of malignancy. Colonoscopy with biopsy showed a resolving patchy colitis sparing the rectum suggesting a resolving ischemia in the inferior mesenteric artery distribution. The patient's history, laboratory evaluation and diagnostic imaging excluded most common causes of pancreatitis. Considering her rapid recovery after discontinuation of metronidazole, it was concluded that this drug was the most likely etiology of her acute pancreatitis.

Discussion

Metronidazole has widespread uses as antiprotozoal, a part of medication regimen for eradication of H. Pylori, for different anaerobic infections and against Clostridium Difficile colitis. Metronidazole diffuses in to nearly all tissues including pancreas. Common adverse effects include reversible neutropenia, metallic taste, urticaria, vaginal and urethral burning, dark urine, nausea, vomiting, anorexia, epigastric pain and disulfiram like reaction with alcohol intake, to name a few. [2]

Metronidazole has been hypothesized to increase the risk of acute pancreatitis. Direct toxic effects of free radicals on pancreatic B cells, together with immunologic damage to pancreatic ducts and adverse metabolic effects through penetration of metronidazole into pancreatic tissue have been implicated in the pathogenesis. [2] It is known that microbial nitroreductases reduce the metronidazole under anaerobic conditions to a cytotoxic radical, which, in turn interacts with DNA causing helical destabilization and strand breakage. [3]

In 1985 Plotnick et al described the first case of metronidazole-associated pancreatitis. The patient was re-challenged with metronidazole 5 weeks after the first pancreatitis episode and suffered a recurrence of disease. [4] Tsesmeli et al reported a case of metronidazole-related acute pancreatitis during a relapse of ulcerative colitis. Conservative measures and discontinuation of metronidazole as well as mesalamine resulted in complete recovery with no recurrence of pancreatitis after re-administration of meselamine. [5] Feola and Thornton reported the recurrence of acute pancreatitis 12 hours after re-challenging a patient with metronidazole for treatment of trichomoniasis. [6] Sura et al described a case of acute pancreatitis in a patient after coronary artery bypass surgery who was treated with metronidazole for suspected post-surgical aspiration pneumonia. [7] In a population based case-control study of 3038 cases of pancreatitis, Nørgaard et al estimated that metronidazole was associated with a 3 fold increase in risk of acute pancreatitis. Risk was higher in patients concomitantly prescribed medication for *Helicobacter pylori* eradication. In spite of the large sample size, interpretation of this study is constrained by the inherent limitations of a case-control design. [8]

Friedman GD and Selby JV, reported that "the upper 95% confidence limit for the occurrence rate of metronidazole induced pancreatitis requiring hospitalization is 3.9/10,000 prescriptions and 4.6/10,000 recipients" the true rates were thought to be lower. It was concluded that severe pancreatitis seems to be a rare adverse reaction to metronidazole. [9] The case reports with the strongest evidence are those that (1) clearly diagnose pancreatitis and exclude common etiologies, (2) provide the dose and time interval between the start of treatment with the suspected drug and the onset of pancreatitis, (3) document response to withdrawal of drug, and (4) demonstrate recurrent pancreatitis on rechallenge with the drug [13]. Although here are only 8 previous case reports of metronidazole induced pancreatitis in the English literature. The drug meets the above criteria and can be classified as having a probable association with the onset of acute pancreatitis. [15,16]. All cases reported, had a moderate self-limited course and only 3 (including our case) had radiographic evidence of acute pancreatitis.

Conclusion

This case provides the ninth report of Metronidazole-induced pancreatitis in the English language literature as shown in Table [1]. All of the cases were reported in females and ran a benign course in continuity with most drug-induced pancreatitis [14]. There was a variable interval between exposure to Metronidazole and development of pancreatitis ranging from 12 hours [6] to 38 days [4], it should therefore be considered in patients presenting after minimal exposure to Metronidazole, in our case just 3 doses. A rechallenge is not to be recommended but this requires early recognition on the part of the clinician. Although uncommon, metronidazole use should be

considered as a potential precipitant in patients presenting with acute pancreatitis. Further evaluation of the subject with a retrospective database cohort study could allow improved estimates of the association of metronidazole and pancreatitis.

Table 1: Metronidazole-induced pancreatitis, reported cases in literature

Author (Reference No.)	Age	Sex	Episode No.	Onset of symptom after starting metronidazole (days)	Indication for using metronidazole
Plotnick et. al (4)	29	F	1st	1	Post-partum vaginitis
			2nd	7	Unspecific vaginitis
Sanford et. al (10)	63	F	1st	7	Crohn's disease
Celifarco et. al. (11)	61	F	1st	4	Aspiration pneumonia
Corey et. al. (12)	49	F	1st	3-5	Trichomoniasis
			2nd	< 1	Trichomoniasis
Sura et. al (7)	23	F	1st	8	Bacterial vaginosis
			2nd	3-7	Bacterial vaginosis
			3rd	3-7	Bacterial vaginosis
			4th	3-7	Bacterial vaginosis
Feola et. al. (6)	22	F	1st	< 1	Vaginosis
			2nd	1	Vaginosis
			3rd	1	Vaginosis
Nigwekar et. al. (1)	46	F	1st	8	Bacterial vaginosis
			2nd	8	Bacterial vaginosis
O'Halloran et al. (17)	25	F	1st	2	Endodontic abscess
			2nd	1	Endodontic abscess

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