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Case Report

Fatal case of acute necrotic pancreatitis secondary to chronic abuse of acetaminophen: a case report

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ABSTRACT

Acetaminophen is a widely used analgesic and antipyretic. It is also known to cause hepatotoxicity and is rarely associated with acute pancreatitis due to overdose. We report the case of a 55-year-old man with no known comorbidities, who presented with severe abdominal pain and vomiting. His medication history revealed chronic abuse of a fixed-dose combination containing 37.5 mg of tramadol hydrochloride and 325 mg acetaminophen 3-6 tablets per day for over 20 years for general body pain without a specific diagnosis. He was diagnosed with acetaminophen-induced acute necrotic pancreatitis after ruling out gallstones and other factors such as alcohol consumption, and family history. Although he got discharged against medical advice, follow-up revealed that he had succumbed to his illness within 15 days. This was a fatal case of acetaminophen-induced pancreatitis due to chronic abuse for over 20 years at a dose of less than 2 g/day. This case highlights the need for periodic monitoring of patients taking acetaminophen at doses within the recommended daily dose.

Keywords: Abuse, Acetaminophen, Acute necrotic pancreatitis, Case report

INTRODUCTION

Acute pancreatitis (AP) is a common disease expressed as an inflammatory injury to the pancreas caused by self-digestion of pancreatic tissue. It is characterized by abdominal pain suggestive of pancreatitis, serum amylase and/or lipase levels at least thrice the normal levels, and characteristic imaging findings. Common etiologies of acute pancreatitis include gallstones, alcohol use, hypertriglyceridemia, hypercalcemia, tumor, and endoscopic retrograde cholangiopancreatography (ERCP).[1] Many drugs have been reported to cause acute pancreatitis, accounting for 0.1-2% of all cases of acute pancreatitis.[2] Although acetaminophen-induced hepatotoxicity is well known, it can also cause pancreatitis.[3,4]

Acute pancreatitis can present with varying severity, and mild pancreatitis is commonly self-limiting; however, severe pancreatitis is associated with the development of complications such as parenchymal or peripancreatic fluid collections, necrosis, and mortality of up to 30%.[1]

This is a severe case of acute necrotic pancreatitis with mild ascites and thrombosis of the retro pancreatic segment of the splenic vein due to 37.5 mg of tramadol hydrochloride and 325 mg acetaminophen fixed-dose combination abuse for over 20 years, where the daily dose was within the limits of dosage recommendations, unlike

many cases where acute pancreatitis was associated with acute overdose, making this case unique.

CASE REPORT

A 55-year-old man presented to the emergency department with complaints of severe abdominal pain and anuria the day before arriving at the hospital. He also complained of vomiting 2-3 episodes per day for one month. A medication history interview conducted by a clinical pharmacist revealed that he would administer a fixed-dose combination containing 37.5 mg tramadol hydrochloride and 325 mg acetaminophen 3-6 tablets every day over 20 years for general body pain with no specific diagnosis. His wife also informed he had no comorbidities and no family history of pancreatitis.

Arterial blood gas (ABG) analysis showed severe metabolic acidosis. After initial stabilization, the patient was transferred to the ICU and was managed with supportive care.

On admission, the white blood cell count was 177000 mm^3 with neutrophilia. The serum amylase level was 272 IU/l, it is more than 1.5 times the upper limit of normal, indicating a poor prognosis. Serum lipase was also elevated i.e.1274 IU/l. The serum triglyceride level was 129 mg/dl, which excluded hypertriglyceridemia as a cause of pancreatitis. Liver function test showed normal total bilirubin (0.6 mg/dl), aspartate aminotransferase (75 IU/l), alanine aminotransferase (28 IU/l), and alkaline phosphatase (368 IU/l). Serum creatinine was elevated i.e. 1.1 mg/dl, and HS troponin-I was 0.024 ng/ml. His 2D Echo showed normal left ventricular ejection fraction (LVEF) of 64%.

On day 2, abdominal contrast-enhanced computed tomography (CECT) revealed acute necrotic pancreatitis with peripancreatic inflammation and fluid collection (Figure 1). CT severity index was 10/10.

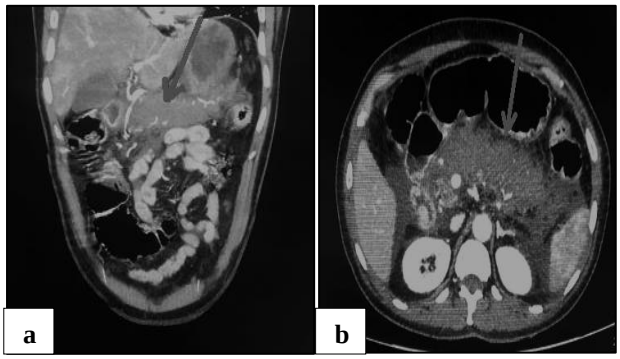

Figure 1: (a) Contrast-enhanced computed tomography scan pointing toward pancreas in arterial and (b) portal phase.

As all the possible etiologies of pancreatitis like alcohol consumption, cholelithiasis, hypertriglyceridemia, hypercalcemia, and trauma were absent, taking into consideration the chronic abuse of acetaminophen the patient was diagnosed with "acetaminophen-induced acute necrotic pancreatitis."

On day 3 of admission after the definitive diagnosis, the patient's family was apprised of his condition. His family requested discharge, and he was discharged against medical advice on day three.

Follow up

A clinical pharmacist contacted the patient via telephone. The patient's wife revealed that he had succumbed to his illness within 15 days.

DISCUSSION

Acetaminophen is a widely used analgesic and antipyretic. It is a component of many fixed-dose combinations of tramadol hydrochloride, ibuprofen, aceclofenac, and diclofenac.

Acetaminophen has minimal anti-inflammatory properties but acts as an analgesic and antipyretic by inhibiting the synthesis of prostaglandins in the central nervous system (CNS) and through other mechanisms in CNS.[5]

Clinical pharmacokinetics

The multiple-dose pharmacokinetics of tramadol hydrochloride and acetaminophen, based on information in the product label of the fixed-dose combination, showed that the bioavailability of tramadol and metabolite M1 was lower than that of tramadol alone, without significant changes in acetaminophen bioavailability. The decrease in the AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1, and 24.2% for (-)-M1. However, the cause of this reduction in bioavailability remains unclear. Although cardiotoxicity was suspected in our patient owing to the chronic use of tramadol, the cardiac function was normal, which could be associated with the decreased bioavailability of tramadol.

Drug-induced acute pancreatitis is often challenging to diagnose owing to the lack of specific laboratory tests and depends on the strategy of excluding all other possible causes. Our patient was diagnosed with acute necrotic pancreatitis based on CECT findings, and the etiology was identified as acetaminophen after ruling out all possible causes. The risk of acetaminophen-induced pancreatitis is higher in males than females and increases with age, with the highest cases among 35-49 years. Although our 55-year-old patient did not fit this age range, increasing age was an important risk factor.[6]

Existing literature on acetaminophen-induced pancreatitis is widely associated with an acute overdose of a minimum of 4–120 g. However, He YH et al reported a case where a 32-year-old female was diagnosed with acetaminophen-

induced acute pancreatitis following administration of a dose of less than 4 g (2600 mg) before presenting to the hospital and had no hepatotoxicity.7 Our patient was administered a dose of less than 2 g (325 mg tablet × 6) for over 20 years before presenting to the hospital. Most of the patients have hepatotoxicity, metabolic acidosis, peripancreatic fluid collection, and necrosis. Our patient presented with metabolic acidosis, mild ascites, thrombosis of the retro pancreatic segment of the splenic vein, and minimal left pleural effusion with a poor prognosis, which highlights progressive damage when abused at low doses.

Hepatotoxicity

Acetaminophen-induced liver injury was predominantly associated with the administration of doses greater than 4 g/day, either intentionally or unintentionally.[4]

Not just the dose but many factors like pattern of drug use, age, nutritional status, alcohol consumption, comorbidities play a crucial role in incidence of acetaminophen induced liver injury. Although our patient was administered a dose of less than 4 g for many years, had an unremarkable normal liver function test, which is congruent with the literature highlighting factors associated with acetaminophen-induced liver injury.[3]

However, the exact mechanism underlying acetaminophen-induced pancreatitis remains unclear. According to Hung et al, several mechanisms have been hypothesized, including immune-mediated direct pancreatic toxicity, pancreatic-duct constriction, the influence of medication on bile flow, thrombosis, metabolic effects, and hypersensitivity.[8] This suggests that the underlying mechanism of acetaminophen-induced hepatotoxicity differs from that of pancreatitis.

A population-based cohort study by Chen SJ et al revealed that the risk of acute pancreatitis in the acetaminophen cohort was significantly higher within a 1-year follow-up comparison cohort (aHR=4.69; 95% CI, 1.01–21.8), and the risk decreased but remained significant after a 1-year follow-up.[6] This finding supports our case, indicating the risk associated with acetaminophen-induced pancreatitis when abused for several years.

Badalov et al categorized acetaminophen as class II based on existing evidence and Naranjo adverse drug reaction probability scale evaluation resulted in a score of 6, indicating that the acute necrotic pancreatitis in this patient was probably due to acetaminophen.

In most cases, the appropriate management of acetaminophen-induced pancreatitis prevented mortality.[7] However, our patient could not be managed in our hospital because he was discharged against medical advice, and follow-up revealed that he could not survive for more than two weeks

CONCLUSION

Acetaminophen-induced pancreatitis can occur at doses of less than 2 g upon chronic use, and can be fatal. All patients with prolonged acetaminophen use, even at doses within the recommended range, should be monitored regularly to prevent fatal complications.

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