Acetaminophen-induced acute pancreatitis: A case report and literature review

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Abstract
Acute pancreatitis is rarely associated with drugs. Acetaminophen overdose is a well-known cause of hepatic toxicity, but drug-induced pancreatitis is rarely reported, especially after mild overdose. A 32-year-old woman presented with nausea and vomiting for 12 h, but no abdominal pain following an overdose of eight Tylenol tablets containing acetaminophen (325 mg acetaminophen per tablet). Laboratory results on admission showed abnormal amylase and lipase levels but completely normal liver function. Magnetic resonance cholangiopancreatography revealed mild swelling of the pancreas without fluid collection around the pancreas. The patient complained of severe abdominal pain five days after admission when attempting to drink water and liquids. Eight days after admission, fluid around the pancreas was observed by computed tomography. The patient was subsequently diagnosed with acetaminophen-induced acute pancreatitis after exclusion of common causes. Routine treatment for pancreatitis and N-acetylcysteine were administered to prevent disease progression. The patient was discharged in good condition.

Key words: Pancreatitis; Cholangiopancreatography; Acetaminophen; Acute pancreatitis; Drug-induced acute pancreatitis

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Core tip: This case shows that a dose of acetaminophen of less than 4 g can cause acute pancreatitis without liver damage, and that the mechanism of pancreatitis is different from that of hepatitis, and acetaminophen-induced acute pancreatitis may not be related to the drug dose. Although drug-induced acute pancreatitis is rare and the detailed underlying mechanism is unknown, physicians should consider this etiology after ruling out other causes of pancreatitis, especially in young women who are at high risk of overdosing on Class I and Class II drugs.

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INTRODUCTION

Acute pancreatitis is a common disease in the clinic, and the mortality rate in patients with severe pancreatitis is high. Biliary stones, alcohol consumption, metabolic disorders and tumors are the most frequent causes of acute pancreatitis. Drug-induced acute pancreatitis is implicated in only a minority of cases, with an incidence of 0.1%-2% [1,3]. To date, over 130 kinds of drugs have been reported to cause acute pancreatitis, including acetaminophen [2]. It is well known that acetaminophen overdose causes hepatic toxicity, but it is a rare cause of acute pancreatitis. Only 11 cases of pancreatitis and hepatic impairment have been associated with acetaminophen at doses ranging from 4 to 120 g. Unlike previous reported cases, we report a case of acute pancreatitis caused by low doses of acetaminophen but without liver damage (Tables 1 and 2).

CASE REPORT

A 32-year-old woman presented with nausea and vomiting for 12 h associated with dizziness and epigastric pain. Before attending the hospital, she took eight Tylenol tablets containing acetaminophen (325 mg acetaminophen per tablet) after quarreling with her husband. She denied taking other drugs, alcohol consumption, gallbladder stones, trauma, autoimmune diseases and diabetes mellitus. The upper abdomen was soft with mild tenderness. Jaundice, hepatospplenomegaly, ascites, and Murphy’s sign were absent.

Laboratory examinations showed the following: Hemoglobin 10.8 g/dL, white blood cells 5.5 × 10^9/L, neutrophils 65%, and platelets 169 × 10^9/L. Abdominal ultrasonography showed no abnormalities in the pancreas. However, magnetic resonance cholangiopancreatography (MRCP) showed that the pancreas was bulky without exudation. In addition to routine treatment for pancreatitis, N-acetylcysteine was administered to the patient to prevent disease progression. Five days after admission, she was able to drink water and take a liquid diet. Her serum amylase level decreased and abdominal pain resolved. However, that night she complained of severe upper abdominal pain radiating to the midcentral back with nausea and hypoglycemia. Contrast-enhanced computed tomography (CT) demonstrated swelling of the pancreas, especially the head of the pancreas, with fluid collection around the pancreas (Figure 1). Therefore, the patient was fasted again. In the following days, abdominal pain gradually alleviated and her diet gradually transitioned to semi-liquids as laboratory examinations revealed serum amylase of 281 U/L and lipase of 263.7 U/L with normal aminotransferase (13 U/L) after three days of pancreatic secretion/enzyme activity suppression and symptomatic treatment. On day 10 after admission, the patient requested early discharge as she had no abdominal pain or other feelings of discomfort. The patient was seen as an outpatient and laboratory examinations revealed serum amylase of 97 U/L and lipase of 15 U/L two weeks later. The patient refused further CT examination.

DISCUSSION

Drug-induced acute pancreatitis is rare with a reported incidence of 0.1%-2%, but should not be overlooked [1,3]. However, drug-induced pancreatitis remains a difficult and challenging diagnosis due to atypical clinical and laboratory tests, which is usually established by excluding other causes. A positive rechallenge is the most effective proof but cannot be performed due to ethical reasons. Our patient took an overdose of a drug containing acetaminophen in a suicide attempt. However, during the follow-up period, the typical conditions associated with acetaminophen overdose did not occur. In general, drug-induced acute pancreatitis is more frequent in children, women, the elderly, and in patients with advanced HIV infection and inflammatory bowel disease [4,5]. A single-center study with about 328 patients with acute pancreatitis from Australia revealed that drug-induced acute pancreatitis appeared to be more common in middle-aged women, which was attributed to the es-
Our patient was a young woman and thus a high-risk individual. Based on the weight of evidence including the presence of a rechallenge, latency, and the number of case reports, Badalov et al [3] divided drugs into five categories including acetaminophen, which was categorized as Class II. It has been reported that drugs belonging to Class I and Class II have the "most evidence" of causing acute pancreatitis as shown by published case reports [2].

Acetaminophen is frequently used for pain and fever in the clinic and is easily obtained from any pharmacy without prescription. Acetaminophen, when taken in an overdose, is a well-known cause of hepatic toxicity, but is rarely the etiologic agent of acute pancreatitis. To date, 11 case reports have been published describing acetaminophen-induced pancreatitis (Table 1) [7-17].

| Year | Age/gender | APAP (g) | Serum APAP | AMS (IU/L) | ALT (IU/L) | TBil | NAC | Ref. |
|------|------------|----------|------------|------------|------------|------|-----|------|
| 1977 | 31/F       | 60       | NA         | 1440       | 300        | H    | No  | [7]  |
| 1977 | 41/F       | 25       | NA         | 1250       | NA         | H    | No  | [8]  |
| 1986 | 34/F       | 25       | 62 μg/mL   | 1500       | 380        | NA   | Yes | [9]  |
| 1991 | 34/F       | 9.37-13  | 77.7 μg/mL | 936        | 225        | NA   | Yes | [10] |
| 1995 | 48/F       | 25       | NA         | 300        | 8700       | NA   | No  | [11] |
| 1997 | 74/F       | NA *     | 31 μg/mL   | 787        | 3070       | H    | Yes | [12] |
| 2001 | 47/M       | 4        | NA         | 498        | 408        | H    | No  | [13] |
| 2009 | 35/F       | 3.97-5.3 b | NA       | 1414       | 75 (H)     | Normal | No | [14] |
| 2009 | 17/F       | 15       | Below      | 529        | Normal     | Normal | No | [15] |
| 2012 | 40/F       | H        | NA *       | NA *       | Normal     | Normal | Yes | [16] |
| 2014 | 19/F       | 78-120   | 208.4 μg/mL | 638       | 9689       | H    | NA  | [17] |

*A detailed medical history was difficult to obtain from this patient due to her confused mental state; *5.97-5.3 g/d for 1 mo; *Abdominal CT showed features suggestive of acute pancreatitis, AMS was not available. APAP: Acetaminophen; AMS: Serum amylase; ALT: Alanine aminotransferase; TBil: Total bilirubin; NA: Not available; NAC: N-acetylcysteine; H: High.

Figure 1  Magnetic resonance cholangiopancreatography and computed tomography findings. A: MRCP shows the bulky pancreas without exudation on admission; B: CT demonstrates swelling of the pancreas, especially the head of the pancreas, with fluid around the pancreas 8 d after admission. MRCP: Magnetic resonance cholangiopancreatography; CT: Computed tomography.
A 32-year-old woman presented with nausea and vomiting for 12 h associated with dizziness and epigastric pain.

### Clinical diagnosis
Acetaminophen-induced acute pancreatitis.

### Differential diagnosis
Biliary pancreatitis, alcohol-induced pancreatitis, hyperlipidemic pancreatitis and codeine-induced pancreatitis.

### Laboratory diagnosis
Laboratory workup revealed a significant elevation of serum amylase of 990 U/L but normal aminotransferases.

### Imaging diagnosis
Magnetic resonance cholangiopancreatography showed that the pancreas was bulky without exudation. Computed tomography demonstrated swelling of the pancreas, especially the head of the pancreas, with fluid collection around the pancreas.

### Treatment
Abrosia, routine treatment for pancreatitis, and N-acetylcysteine were administered.

### Related reports
A total of eleven cases of acetaminophen-induced acute pancreatitis have been reported in the literature. Among these cases, the frequency and single overdose of acetaminophen were related to pancreatic toxicity. Unfortunately, no adequate evidence-based basis has been found because understanding of drug-induced acute pancreatitis is largely based on case reports and critical reviews.

This patient was fortunately taken to the hospital in time and treated with N-acetylcysteine, which can prevent hepatotoxicity following acetaminophen overdose by replenishing hepatic glutathione stores. In patients who receive N-acetylcysteine within the first eight hours after an acute overdose, the risk of hepatotoxicity is less than 5%, whereas delays beyond 10 h are associated with an increased risk of hepatic injury [20]. In other cases, they either took a large dose of acetaminophen or did not receive timely treatment, or they were patients at high risk, such as those with known alcohol consumption, which may have led to drug-induced pancreatitis with different levels of liver damage.

In conclusion, less than 4 g acetaminophen can cause acute pancreatitis without liver damage, which indicates that the mechanism of pancreatitis is different from that of hepatitis, and the severity of acute pancreatitis may not have a reliable dose-dependent relationship. Although drug-induced acute pancreatitis is rare and easily ignored, we should be aware of this condition in high-risk patients with a history of drug overdose, especially Class I and Class II drugs, and both timely and appropriate treatment should be administered.

### Table 2 Causes of acute pancreatitis

| Causes of acute pancreatitis |
|-----------------------------|
| Common causes               |
| Gallstones, alcohol misuse, hyperlipidemia |
| Hypercalcemia, autoimmune, idiopathic, drugs, trauma, tumor |
| Other causes                |

**ARTICLE HIGHLIGHTS**

**Case characteristics**
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**Laboratory diagnosis**
Laboratory workup revealed a significant elevation of serum amylase of 990 U/L but normal aminotransferases.

**Imaging diagnosis**
Magnetic resonance cholangiopancreatography showed that the pancreas was bulky without exudation. Computed tomography demonstrated swelling of the pancreas, especially the head of the pancreas, with fluid collection around the pancreas.

**Treatment**
Abrosia, routine treatment for pancreatitis, and N-acetylcysteine were administered to the patient.

**Related reports**
A total of eleven cases of acetaminophen-induced acute pancreatitis have been reported in the literature.
reported in the literature but this case took the lowest dose of acetaminophen without liver damage.

Experiences and lessons
Acetaminophen-induced acute pancreatitis is rare and should be considered in the differential diagnosis of acute pancreatitis, especially in high-risk patients with an overdose of suspected drugs.

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