Acute fulminant drug induced necrotizing pancreatitis in a patient with ankylosing spondylitis

Pancreatitis necrotizante aguda fulminante secundaria a fármacos en un paciente con espondilitis anquilosante

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Abstract

Drug-induced acute necrotizing pancreatitis is a rare adverse event, although it has been reported in association with different drugs. Clinical cases of acute pancreatitis complicating treatment with anti-TNF-α such as infliximab have been exceptionally reported. We describe a patient with ankylosing spondylitis treated with etanercept who developed an acute fulminant necrotizing pancreatitis that resulted in death.

Key words: acute pancreatitis; etanercept; anti-TNF-α agents; ankylosing spondylitis.

Introduction

Drug-induced acute necrotizing pancreatitis is a rare adverse event, and it has been reported in association with different drugs1-3. Clinical cases of acute pancreatitis complicating treatment with anti-TNF-α such as infliximab have been exceptionally reported4. Contrarily, an ameliorating effect of anti-TNF-α agents on experimentally-induced acute pancreatitis in animal models has been reported5-8. We describe a patient with ankylosing spondylitis treated with etanercept who developed an acute fulminant necrotizing pancreatitis that resulted in death.

Case report

A 57-year-old man was admitted to the emergency department because of epigastric pain of one week’s duration. The patient was diagnosed of ankylosing spondylitis at the age of 27 and he was treated with repeated courses of NSAIDs to which etanercept was finally added due to lack of efficacy. Six months after starting anti-TNF-α therapy the disease was inactive and the patient only took indomethacin sporadically with omeprazole for gastric protection. He did not have a history of dyslipidemia or alcohol consumption. Abdominal pain was unrelated to food intake and was not accompanied by nausea, vomiting, or changes in the bowel habits. Physical examination revealed mucocutaneous jaundice and pain in the epigastrium on deep palpation without signs of peritoneal irritation. Laboratory tests on admission showed a serum bilirubin level of 6.3 mg/dL (direct bilirubin 3.6 mg/dL), alkaline phosphatase 177 mg/dL, aspartate aminotransferase 470 mg/dL, and alanine aminotransferase 430 mg/dL. The serum lipid profile, ions and amylase in serum and urine were within normal ranges. The abdominal ultrasound and computed tomography (CT) scan were unrevealing. An upper gastrointestinal endoscopy was normal. Treatment with etanercept was stopped and the patient was given ketorolac for pain relief and pantoprazole. Seven days after admission, the same pattern of abdominal pain persisted and became more severe. The serum amylase level was 2013 mg/dL and urine amylase 29,000 mg/dL. Abdominal ultrasound revealed an enlarged pancreatic gland with ill-defined borders. An urgent CT scanning showed suggestive signs of necrotizing pancreatitis (Figure 1). Serological tests for infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus and Epstein-Barr virus were negative. Antinuclear antibodies, anti-LKM-1 and antimitochondrial antibodies were also negative. A magnetic resonance cholangiography to exclude microthiasis was not performed because the patient was wearing a knee prosthesis. An exploratory laparotomy was performed, revealing a markedly enlarged pancreas of inflammatory aspect spreading towards the duodenum and the common bile duct. The histopathologic study showed steatonecrosis.

Figure 1. The abdominal CT scan showed an increase in the pancreatic volume, with areas of necrosis and peripancreatic fluid, without evidence of cholelithiasis or pancreatic calcifications

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Acute pancreatitis typically presents as an acute inflammation of the pancreas that may or may not involve the surrounding tissues. Gallstones and heavy alcohol use are major causes of this condition. Other common causes include trauma, pancreatic tumors, surgery, hypertriglyceridemia, endoscopic retrograde choledangiopancreatography and hyperparathyroidism. Drug-induced acute pancreatitis ranges from between 0.1 and 2%. Different classifications of drugs commonly associated with acute pancreatitis have been proposed. Using criteria based on the presence of a rechallenge, latency, and the number of the cases reports (Table 1), a classification system “based on the evidence” was provided. Table 2 shows the medications from the published case reports with the “most evidence” of causing acute pancreatitis. There is no clear mechanism by which drugs cause pancreatitis, although they appear to induce pancreatitis by direct or indirect effects or a combination of both. Direct effects include toxic effects (diuretics, steroids) or hypersensitivity reactions (azathioprine, aspirin, salicylates), while indirect mechanisms consist of ischemia (diuretics, azathioprine) or intravascular thrombosis (steroids).

A number of drugs used to treat rheumatologic diseases can trigger acute pancreatitis. Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. Our patient, however, also received other medications described to induce acute pancreatitis, such as indomethacin and omeprazole prior to the episode of acute pancreatitis, and ketorolac together with pantoprazole during hospital admission. Although the duration of treatment with etanercept of 6 months may be too long for a cause-effect relationship, the implication of etanercept as the causative drug of acute pancreatitis cannot be excluded. In conclusion, we present a patient who developed a fulminant acute necrotizing pancreatitis and had a fatal outcome, plausibly associated with drug-induced pancreatitis. Due to the rarity of this adverse event doctors should pay close attention to patients taking this kind of drugs in which a complaint of abdominal pain lasting for several days with no apparent cause may require a prompt referral for medical consultation.

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References

Table 1. Classification of drug induced pancreatitis.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs.</td>
</tr>
<tr>
<td>Ib</td>
<td>At least 1 case report with positive rechallenge, however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out.</td>
</tr>
<tr>
<td>II</td>
<td>At least 4 cases in the literature. Consistent latency (75% of cases).</td>
</tr>
<tr>
<td>III</td>
<td>At least 2 cases in the literature. No consistent latency among cases. No rechallenge.</td>
</tr>
<tr>
<td>IV</td>
<td>Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge.</td>
</tr>
</tbody>
</table>

Table 2. Summary of drug-induced acute pancreatitis.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Acetylsalicylate, bezafibrate, cannabis, carbimazole, codeine, cytoxan, arabinoside, dapsone, enalapril, furosemide, ionezid, melsemial, metioniloxil, pentamidine, pravastatin, procanamid, pyridinol, simvastatin, stilbogluconate, sulfamethoxazole, sulindac, thioucyline, etopic acid</td>
</tr>
<tr>
<td>Ib</td>
<td>At least 2 cases in the literature, without rechallenge.</td>
</tr>
<tr>
<td>III</td>
<td>At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out.</td>
</tr>
<tr>
<td>IV</td>
<td>Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge.</td>
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