Simvastatin-Induced Acute Pancreatitis: A rare side effect of a statin

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Acute Pancreatitis is defined as the abrupt nonbacterial inflammation of the pancreas. Typical symptoms comprise of abdominal pain located in the epigastrium and radiating to the back. In the majority of cases, the progression of acute pancreatitis is mild and self-limited. Albeit, one fifth of patients may deteriorate and develop multiple organ dysfunction syndrome (MODS) which eventually enhance smortality rate.[1,2] The first and second most common etiologies, accounting for approximately 75% of cases in most developed countries, are gallstones and alcohol respectively.[3] Less common causes include pancreatitis occurring after endoscopic retrograde cholangiopancreatography (ERCP), abdominal trauma, familial hypertriglyceridemia, hypercalcemia, autoimmune disease, toxins, etc.[4,5] Drug-induced pancreatitis is a relatively rare occurrence, accounting for approximately 1.2-2% of cases.[6-8] Of those, acute pancreatitis caused by the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, often referred to as statins, has been reported rarely.[9] We reported a case experiencing the very rare side effect of simvastatin-associated acute pancreatitis. This information should increase awareness of physicians and pharmacists not to overlook the etiology particularly in any patients diagnosed with idiopathic pancreatitis.

Case Report

An 84-year-old Thai man was admitted to hospital outside Bangkok on April 15, 2013 (Day 1) due to acute epigastric pain radiating to the middle of the back, without nausea or vomiting. The attack occurred after dinner and lasted for 10 hours prior to admission. He had underlying diseases of hypertension (HT), coronary artery disease (CAD), and hypertrophy of the prostate gland and these conditions were well-controlled by oral medications including simvastatin (40 mg once daily), aspirin (81 mg once daily), amlodipine (5 mg once daily), trimetazidine hydrochloride (35 mg twice a day), and alfuzosin (10 mg once daily). He had been taking these medications since diagnoses were made in 2007. Alcohol consumption was stopped more than 10 years previously.

On physical examination, the patient was alert. Vital signs: BP 120/70 mmHg, HR 80/min, T 37.8°C, RR 22/min. Body mass index was 26.1 kg/m^2. The cardiopulmonary system was unremarkable. Abdominal examination revealed no guarding but with generalized rebound tenderness; hepatosplenomegaly could not be detected. There was no cutaneous sign of chronic liver disease.

Hematologic studies revealed the following findings: pancreatic amylase (P-amylase) 2,598 U/L (normal: 8-53 U/L), no lipase level performed before transfer, total bilirubin 2.8 mg/dL (normal: 0-1.5 mg/dL), direct bilirubin 2.1 mg/dL (normal: 0-0.5 mg/dL), aspartate aminotransferase (AST) 136 U/L (normal: 0-40 U/L), alanine

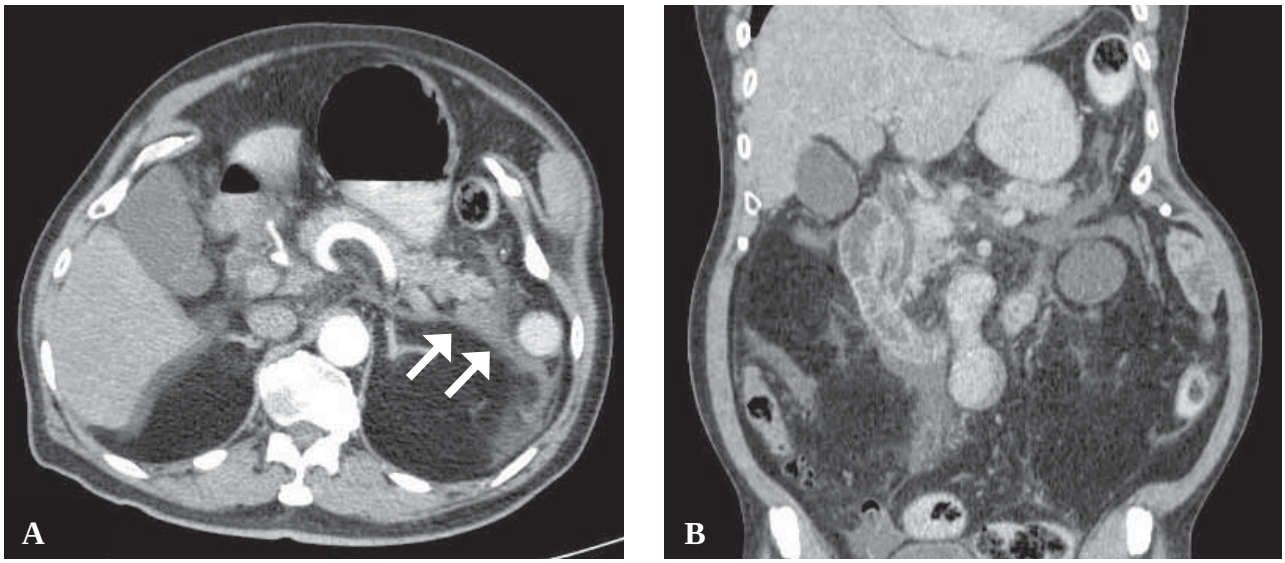

Figure 1: *MDCT of the upper abdomen with contrast enhancement, axial section reveals:*
A. infiltration of the peripancreatic fat planes (see arrows) central, dorsal and left anterior renal fascia, while the pancreas itself appears unremarkable.
B. normal gallbladder and common bile duct.

aminotransferase (ALT) 112 U/L (normal: 0-40 U/L), cholesterol 112 mg/dL (normal: < 200 mg/dL), triglyceride 49 mg/dL (normal: < 150 mg/dL), troponin-T 0.006 ng/mL (normal: 0-0.014 ng/mL), carcinoembryonic antigen (CEA) 1.85 ng/mL (normal: 0-3.8 ng/mL), CA 19-9 (digestive tract) 26.41 U/mL (normal: 0-37 U/mL). Complete blood count, alkaline phosphatase (ALP), and hepatitis serologies were unremarkable. Blood culture was taken.

Multidetector computed tomography (MDCT) of the whole abdomen demonstrated diffuse enlargement of the pancreas with fluid infiltrating along peripancreatic and bilateral anterior pararenal spaces; dilatation of the intrahepatic bile ducts down to the common bile duct, 11 mm in maximal diameter with suspected thickening of the periampullary region. The gallbladder was well-distended without gallstones. These findings were compatible with acute non-necrotizing pancreatitis. (Figure 1)

Symptomatic and supportive treatments were provided including adequate hydration and nutrition, pain management using meperidine hydrochloride (Pethidine®), maintaining equilibrium of body fluid and electrolytes. Due to fever and since infectious causes could not be entirely excluded, empirical antibiotics (ceftriaxone and metrodinazole) were administered. With regard to drug - associated acute pancreatitis, all regular medications had been withheld since admission to the referring hospital prior to his arrival at BMC.

On Day 3 of admission, patient was clinically improved: no fever, increased appetite, and disappearance of abdominal symptoms and signs. Blood culture showed no organism growth within 72 hours, therefore antibiotics were discontinued. Blood tests showed decrement of P-amylase levels (401 U/L), AST (38 U/L), and ALT (60 U/L). Blood for lipase showed a high level of 259 U/L (normal: 0-190 U/L). However, to avoid comorbidities that could be caused by underlying diseases of HT and CAD, all withheld oral medications- except simvastatin - were restarted on that day.

On Day 5, two days after restarting these medications, blood tests for both P-amylase and lipase showed normal values of 96 and 74 U/L respectively.

On Day 7 with normal level of P-amylase of 86 U/L, patient was discharged. Simvastatin was not prescribed.

On Day 12, five days after discharge, at follow up, he was clinically well without abdominal pain or jaundice. Serum P-amylase was followed and was found to be normal.

Discussion

The diagnosis of acute pancreatitis, according to the guidelines of the American College of Gastroenterology, requires at least two from three of the following criteria: 1) characteristic abdominal pain, 2) elevation level of serum amylase and/or lipase (≥ 3 times the upper normal limit), and 3) characteristic findings of acute pancreatitis on CT scan. Our patient had clinically and radiographically fulfilled the diagnostic criteria: classic abdominal pain, high serum level of amylase more than 3 times of upper limits, and MDCT (which is the best imaging technique for diagnosis of acute pancreatitis) which displayed typical findings comprising of enlargement of the pancreas with diffuse edema with peripancreatic fluid collections.[1, 10-12]

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Table 1: Series of blood tests from admission to hospital discharge and follow up visit.

Test / DAY	Normal range	DAY 1 (Admission)	DAY 3* (Restarted medictions)	DAY 5	DAY 7 (Discharge)	DAY 12 (Follow up)
P-Amylase	28-100 Unit/L	2598	401	96	86	80
Lipase	0-190 Unit/L	N/A**	259	74	N/A	N/A
Total Bilirubin	0-1.5 mg/dL	2.8	N/A	N/A	N/A	N/A
Direct Bilirubin	0-0.5 mg/dL	2.1	N/A	N/A	N/A	N/A
AST	0-40 Unit/L	136	38	30	N/A	N/A
ALT	0-40 Unit/L	112	60	34	N/A	N/A

*DAY 3 = Day of restart withheld medications except simvastatin; **N/A = not applicable.

Table 2: Classification system of medication-associated acute pancreatitis[13]

Categories	Definition
Class Ia	Medications at least one case report Evidence of a positive rechallenge Exclusion of other causes of acute pancreatitis
Class Ib	Similar to class Ia but other causes of acute pancreatitis could not be excluded
Class II	Medications at least four case reports Consistent latency period for at least 75% of the cases
Class III	Medications at least two case reports Do not have rechallenge data or a consistent latency period
Class IV	Medications have one case report without rechallenge data

Specifying the etiology of acute pancreatitis is crucial. Due to common causes e.g. gallstones, alcohol, a history of ERCP, hypertriglyceridemia, autoimmune having been excluded, there was thus a suspicion of medication-associated pancreatitis. Some medical literaturef has reported and listed a panel of drug-induced acute pancreatitis.[7,8, 13-17] Looking at the regular medications used by our patient, aspirin,[14,18] amlodipine,[14,18] and simvastatin[13,14,18,19] have all been identified as causes of acute pancreatitis. After carefully determining risks and advantages between underlying diseases and restart of medications, all withheld drugs but simvastatin were re-challenged. Patient was closely observed and monitored which revealed clinical improvement and serum P-amylase returned to normal. According to this information, pancreatitis induced by aspirin, amlodipine, trimetazidine hydrochloride, and alfuzosin were ruled out. Therefore, by exclusion of other possible medications, the etiology of simvastatin-induced acute pancreatitis was confirmed.

Drug-associated acute pancreatitis has been classified into five categories: Ia, Ib, II, III, and IV based on the number of case reports, available rechallenge data, consistent latency period, and ability to exclude other causes of acute pancreatitis (Table 2). Statins or HMG-CoA reductase inhibitors have been suggested as a class effect, and they are categorized as class Ia, Ib, III, and IV.[13, 20]

Until recently, the mechanism of action for statin-associated acute pancreatitis was limited and not quite clear. It had been reported as both dose-independent and unpredictable.[21] Because of lacking a consistent latency period, statins are possibly directly toxic to the pancreas causing accumulation of a toxic metabolite that eventually induces acute pancreatitis.[19-21] Other mechanisms are reckoned to be associated with drug interactions through CYP3A4, and/or related to rhabdomyolysis or myalgia that occurred before development of acute pancreatitis.[21, 22] Onset of symptoms can develop from hours to years after commencing statins.[23-26] Similar to our patient, symptoms of acute pancreatitis developed only after taking simvastatin for approximately 7 years.

Regarding prognosis, fortunately the progression of acute pancreatitis in the majority of cases is mild and self-limited.[1] The overall mortality in acute pancreatitis is 5% (3% in the interstitial pancreatitis, 17% in necrotizing pancreatitis).[27-46] However, the mortality rate is close to 0 among patients who develop acute pancreatitis but no multiple organ dysfunction syndrome (MODS).[31, 38, 47, 48]

Conclusion

It is a great challenge for physicians and pharmacists to declare the diagnosis of drug-induced acute pancreatitis. Even if common etiologies of pancreatitis such as gallstones, alcohol, history of ERCP, hypertriglyceridemia, toxin, etc. have already been excluded, **'idiopathic'** (an undiscovered, underlying etiology) pancreatitis should not be finalized unless such a very rare side effect of medications can be excluded. An HMG-CoA reductase inhibitor such as simvastatin is commonly prescribed not only for patients with hyperlipidemia but also for patients with CAD. This medication should be considered as a possible cause of statin-associated acute pancreatitis even if the abovementioned side effect is infrequently reported.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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