

A case of azathioprine-related acute pancreatitis and drug-induced acute pancreatitis

Azatiyoprin ilişkili bir akut pankreatit olgusu ve ilaç-ilişkili akut pankreatit

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ABSTRACT

Acute pancreatitis (AP) is an inflammatory condition, characterized by elevated levels of amylase and lipase, with manifestation of abdominal pain and acute abdomen, and high mortality and morbidity rates. The most common causes of AP other than gallbladder stones and alcohol include hypercalcemia, infections, hypercalcemia, and drugs. One such drug associated with AP is azathioprine. Azathioprine is used to prevent acute exacerbations in Crohn's disease. Herein, we present a case of azathioprine-related AP in a patient with Crohn's disease.

Keywords: Acute pancreatitis, azathioprine, drug

ÖZ

Akut pankreatit (AP), amilaz ve lipaz düzeylerinin yüksekliği ile karakterize, karın ağrısı ve akut batin tablosu izlenen ve mortalite ve morbidite oranları yüksek enflamatuvar bir tablodur. Akut pankreatitin en sık nedenleri arasında safra kesesi taşı ve alkol dışında hiperlipidemi, enfeksiyonlar, hiperkalsemi ve ilaçlar sayılabilir. Akut pankreatit ile ilişkili ilaçlardan biri de azatiopurindir. Azatiopurin, Crohn hastalığında akut alevlenmenin önlenmesinde kullanılmaktadır. Burada Crohn hastalığı olan bir hastada azatiyoprin ile ilişkili bir AP olgusu sunuldu.

Anahtar sözcükler: Akut pankreatit, azatiyoprin, ilaç

Acute pancreatitis (AP) is an inflammatory condition, characterized by elevated levels of amylase and lipase, with manifestation of abdominal pain and acute abdomen, and high mortality and morbidity rates.^[1] According to etiology of acute pancreatitis, while gallbladder stones and alcohol are foremost, other causes include hyperlipidemia, infections, hypercalcemia, drug use, and autoimmunity.^[2] Drug-induced acute pancreatitis (DIAP) accounts for about 2% of AP and is generally of mild-moderate severity.^[3] Acetaminophen, cortisone, metronidazole, azathioprine (AZT), mercaptopurine, and thiazide are some of the

most common drugs that cause AP; drugs associated with AP are presented in Table 1.^[3,4] Chron's disease (CD) is a chronic, idiopathic, inflammatory, bowel disease. A purine analogue, AZT, is used in preventing acute exacerbations of Crohn's disease. Acute pancreatitis is also among the adverse effects of AZT.^[5] Herein, we present an AP case associated with AZT.

CASE REPORT

A 28-year-old female patient presented to our emergency department with belt-like abdominal

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Table 1. Drug-induced acute pancreatitis

ACE Inhibitor	Cyproheptadine	Linagliptin	Liraglutide
Macrolides	Rifapentine	Acetaminophen	Cytosine
Mefenamic acid	Rivastigmine	ACTH	Danazol
6-MP	Ropinirole	Alendronate	Dapsone
Mesalamine	Saw palmetto	Saxagliptin	All-trans-retinoic acid
Alogliptin	DDP-4 inhibitors	Metformin	SSRIs
Alpha-methyl dopa	Diazoxide	Methimazole	Sirolimus
Sitagliptin	Aminosaliculates	Diphenoxylate	Methyl dopa
Sodium stibogluconate	Amiodarone	Dipyridamole	Divalproex sodium
Metronidazole	Somatropin	Amlodipine	Doxercalciferol
Mirtazapine	Statins	Ampicillin	Doxorubicin
Montelukast	Sulfamethoxazole	Antivirals	Ertapenem
Mycophenolate	Sulfasalazine	Aspirin	Estrogens
Exenatide	Nitrofurantoin	Sumatriptan	Atypical antipsychotics
Fibrates	NSAIDs	Tacrolimus	Azathioprine
Finasteride	Octreotide	Tamoxifen	Bupropion
Fluoroquinolones	Paclitaxel	Tetracyclines	Calcitriol
5-Fluorouracil	Pegaspargase	Thiazide diuretics	Cannabis
Furosemide	Penicillin	Thrombolytic agents	Capecitabine
Gabapentin	Pentamidine	TNF-alpha inhibitors	Carbamazepine
GLP-1 analogs	Pergolide	Topiramate	Ceftriaxone
Gold	Phenolphthalein	Valproic acid	Cimetidine
HAART agents	Pilocarpine	Venlafaxine	Cisplatin
Ifosfamide	Prazosin	Vincristine	Clomiphene
Indomethacin	Procainamide	Voriconazole	Codeine
Interferon/ribavirin	Propofol	Zolmitriptan	Colchicine
Interleukin-2	Propoxyphene	Corticosteroids	Irbesartan
PPIs	Co-trimoxazole	Isoniazid	Quinupristin/dalfopristin
COX-2 inhibitors	Isotretinoin	Ranitidine	Cyclophosphamide
Lamotrigine	Repaglinide	Cyclosporine	L-asparaginase

ACE: Angiotensin-converting enzyme; ACTH: Adrenocorticotropic hormone; Rifampin 6-MP: 6-mercaptopurine; DDP-4: Dipeptidyl peptidase 4; SSRIs: Selective serotonin reuptake inhibitors; NSAIDs: Nonsteroidal antiinflammatory drugs; TNF: Tumor necrosis factor; GLP-1: Glucagon-like peptide-1; HAART: Highly active antiretroviral therapy; PPI: Proton pump inhibitor; COX: Cyclooxygenase.

pain. The belt-like sudden onset pain also radiated to the back. The patients physical examination was as follows: general appearance was good, consciousness, cooperation, and orientation was normal, blood pressure: 120/80 mmHg, pulse: 76 bpm, temperature: 37.5°C, abdomen had widespread tenderness but no rebound or defense. The patient was diagnosed with CD two months prior and had begun budesonide/AZT treatment, but it was learned that the patient used only budesonide and used AZT for only 12 days. The patient had no history of alcohol or smoking. According to laboratory tests: WBC: 12,800/mm³, platelet: 250,000/mm³, hemoglobin: 12.4 g/dL,

glucose: 105 mg/dL, urea: 9 mg/dL, creatinine: 0.7 mg/dL, aspartate aminotransferase: 11 U/L, alanine aminotransferase: 14 U/L, gamma glutamyl transferase: 13 U/L, alkaline phosphatase: 46 IU/L, total bilirubin: 0.8 mg/dL, direct bilirubin: 0.1 mg/dL, amylase: 1,276 U/L, lipase: 2,988 U/L, sodium: 137 mEq/L, potassium: 3.9 mEq/L, calcium: 9.3 mg/dL, lactate dehydrogenase: 258 mg/dL, C-reactive protein: 5.2 mg/dL. Chest X-ray was unremarkable. Abdomen ultrasound revealed thickening of the caecum-terminal ileum wall at the ileocecal valve level, changes consistent with edema-inflammation of surrounding mesenteric fatty tissue, and a few

millimetric mesenteric lymph node. The patient with known CD had no pathology other than exacerbation of symptoms. The patient was hospitalized in the internal medicine inpatient service with AP diagnosis. Oral intake was stopped, AZT and budesonide were discontinued, and hydration treatment was initiated. The patient's Ranson score was calculated as 1 point. In terms of etiology, triglyceride was detected as 58 mg/dL and gallbladder stone, alcohol use, hypertriglyceridemia, and hypercalcemia were ruled out. Drug-induced acute pancreatitis was considered foremost. The fact that the patient using budesonide developed AP after starting AZT and that AZT more frequently causes AP compared to budesonide led us to believe that our case was AP induced by AZT. Blood tests performed in the 48th hour of treatment showed amylase: 932 U/L and lipase: 1862 U/L, pain regressed and there was no need to repeat abdomen tomography. On the fourth day of treatment pain had completely resolved, amylase: 168 U/L, lipase: 218 U/L, and CRP regressed to 0.8 mg/dL; the patient was initiated budesonide and mesalamine by gastroenterology, discharged and called for outpatient follow-up.

DISCUSSION

Acute pancreatitis is a severe clinical condition with mortality rate varying between 1-30%.^[6] A study^[7] on the prevalence of drug-induced acute pancreatitis report rates of approximately 8%, while a study from our country reported^[8] a rate of 10%. In a study by Eland et al.,^[9] drugs such as AZT, cimetidine, interferon-alpha, methyldopa, metronidazole, olsalazine, and oxyphenbutazone were reported to be definitely associated with AP. Later studies reported over 50 more drugs other than these that were associated with AP.^[3] Although it is not known exactly how drugs cause AP, the cytotoxic effects of drugs are thought to be caused by mechanisms such as biliary construction, accumulation of toxic metabolites, and hypersensitivity. Drug-induced acute pancreatitis is diagnosed by drug provocation test. If AP reoccurs, definite diagnosis of DIAP is made.^[10]

The literature reports AP risk is eight times higher in patients using AZT.^[11] Acute pancreatitis associated with AZT was first reported in 1972.^[12] AZT-induced AP is generally mild and rarely causes pancreas necrosis.^[13]

Our patient was diagnosed with CD two months prior and was initiated AZT/budesonide, however, the patient began AZT much later. Acute pancreatitis was detected 12 days after our patient began AZT. Drug-induced acute pancreatitis diagnosis, as in other AP causes, is made by excluding other causes.^[14] Causes such as gallbladder stones, alcohol, hypertriglyceridemia, and hypercalcemia were also ruled out in our patient.^[15] The fact that the patient also using budesonide developed AP after starting AZT and that AZT more frequently causes AP compared to budesonide led us to believe that our case was AP induced by AZT.

Although azathioprine-induced AP is known to be mild, cases of severe AP and pancreas necrosis have been reported in the literature.^[13,16] Our case had a mild course in accordance with the literature and showed clinical improvement on the third day. Acute pancreatitis generally develops three to six weeks after start of AZT.^[15] In one case reported AZT-induced AP on the 10th day.^[17] In our patient, AP was detected on the 12th day of treatment. AZT is contraindicated in patients who develop AZT-induced AP and absolutely should not be used.^[18] In our patient budesonide/mesalamine was initiated and AP did not redevelop in follow-up.

In conclusion, it should be kept in mind that AZT frequently causes AP, patients using AZT should be cautious in terms of AP and should immediately seek medical care if they develop clinical symptoms indicative of AP.

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