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CASE REPORT

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Acute pancreatitis associated with multibacillary polychemotherapy for leprosy

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ABSTRACT

Acute pancreatitis (AP) is an inflammatory disease associated with abdominal pain and elevated serum pancreatic enzymes. The most common etiologies are gallstones and alcoholism. Drug-induced AP is quite rare, lacks a solid understanding and has been occasionally reported. The diagnosis requires a great suspicion and a careful exclusion of other causes. We present a case of a 37-year-old man, previously diagnosed with leprosy that developed acute pancreatitis after starting the multibacillary polychemotherapy (PCT/MB). After a month of treatment and the discontinuation of the PCT/MB, the therapy was restarted and a new episode of AP occurred. Three months after this last episode, the PCT/MB was reintroduced, changing one of the medications and the patient had no recurrence of AP or other reactions. Therefore, it is important to take into account that there is a risk of acute pancreatitis in patients on multidrug therapy (MDT) for leprosy.

KEYWORDS: Pancreatitis. Leprosy. Multibaccilary polychemotherapy. Dapsone. Rifampicin.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease associated with abdominal pain and elevated serum pancreatic enzymes. Gallstones and alcoholism are the most common causes of AP[1,2]. Other less frequent etiologies include hypertriglyceridemia, hypercalcemia, fibrosis, autoimmune diseases, toxins and some drugs. AP is commonly mild and self-limited, but some patients may develop a rapidly progressive inflammatory response with significant organ dysfunction and local complications, such as necrosis, abscess or pseudocyst formation[2,3]. Severity and prognosis of acute pancreatitis may be assessed by Ranson's criteria, the Bedside Index of Severity in Acute Pancreatitis (BISAP) score and the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II). These scoring systems provide a multifactorial decision regarding the need for intensive care, based on clinical and laboratory parameters, such as age, admission time, leukometry, drop of the hematocrit, elevation of liver enzymes, elevation of lactic dehydrogenase (DHL) and of blood urea nitrogen (BUN)[4].

Drug-induced AP is quite rare, with an incidence of 2% and it lacks a solid understanding, mainly because the majority of information result from occasional case reports[3]. The diagnosis requires a great suspicion and a careful exclusion of other causes. In the last century, more than 525 drugs possibly associated with acute pancreatitis have been reported to the World Health Organization[2]. Nine cases of acute pancreatitis associated with medications for the multidrug therapy of leprosy

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were reported. Five of these cases were of patients using dapsone, with similar dosage to the PCT/MB, while four cases are related to the use of rifampicin in higher doses[5-13].

We report a case of an acute pancreatitis associated with polichemotherapy for the treatment of multibacilary leprosy.

CASE REPORT

A previously healthy 37-year-old man presented chronic distal paresthesia and areas of reduced hair density, in addition to thermal anesthesia on his back and right leg.

After three weeks of PCT/MB (rifampicin 600 mg monthly; dapsone 100 mg daily; along with clofazimine 50 mg daily and 300 mg monthly), the patient presented with several days of worsening of a left upper quadrant abdominal pain that radiated to the back. Laboratory tests revealed elevated serum amylase 354 U/L, lipase 130 U/L (Figure 1), neutrophils 8,550/mm^3, lactate dehydrogenase (LDH) 264 U/L, C-reactive protein (CRP) 46 mg/L and erythrocyte sedimentation rate (ESR) 25 mm/h. Liver enzymes and kidney function were normal. Imaging studies showed a parenchymal edema affecting the tail and the body of the pancreas, as well as minor changes in other organs, including biliary sludge without cholelithiasis (Table 1). Leprosy medications were suspended and the received intravenous hydration, analgesia, bowel resting drugs and systemic antibiotic therapy (metronidazole and clindamycin).

The patient clinically improved and was discharged after eight days of hospitalization. One month later, PCT/MB was reintroduced with the same medications and doses. In less than 24 h following the medications intake, a rapidly worsening abdominal pain reappeared. Laboratory and imaging tests showed similar findings, including elevated serum amylase 306 U/L, lipase 550 U/L (Figure 1) and pancreatic edema (Table 1). The clinical course and management were also similar and after almost three weeks the patient was discharged again. He lost 11 kg of weight in three months since the first hospitalization.

Three months after the second hospital discharge, the polychemotherapy was resumed. Ofloxacin (400 mg/d) replaced dapsone and the rest of the drugs were maintained with the same posology. Within a month, the patient had no recurrence of the pancreatitis.

The patient had no history of pancreatitis, pancreatic adenocarcinoma, cholelithiasis, cholecystitis, alcoholism and denied the use of alcohol in the last year and during the MDT, abdominal trauma or previous treatment with rifampicin, dapsone or clofazimine.

DISCUSSION

AP usually presents with an upper abdominal pain radiating to the back, nausea, elevated serum pancreatic enzymes and pancreatic edema. AP may be induced by medications, including dapsone and rifampicin. Dapsone has strong evidence implicating it as a cause of AP in this case, since recurrence after a rechallenge with the drug has been reported. However, the association of rifampicin with AP is weaker, considering that there was neither a rechallenge or a consistent latency among cases[1,3,5].

Dapsone-induced AP has been reported with daily

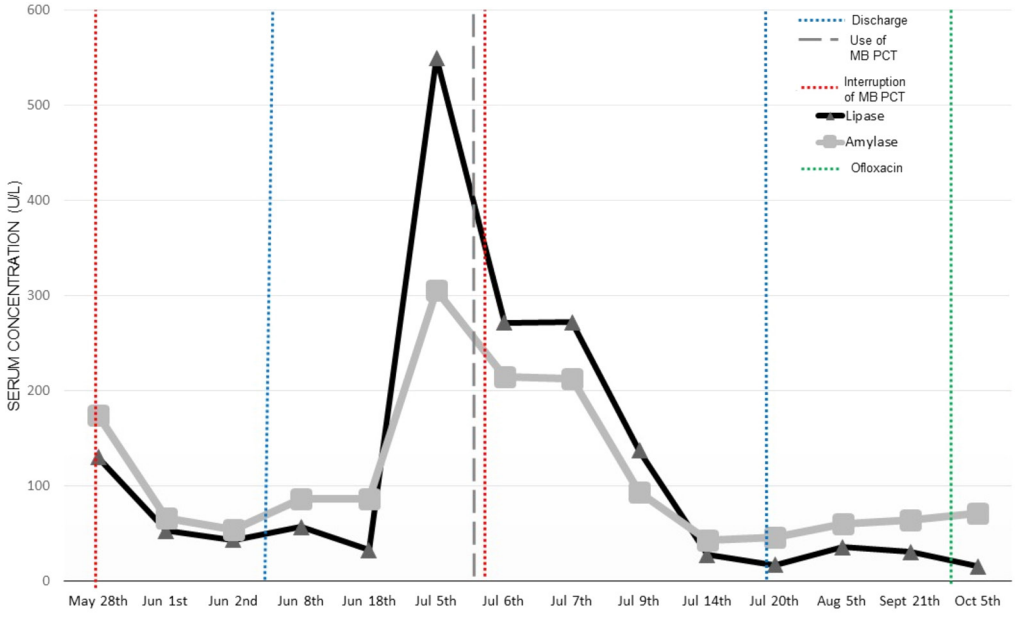

Figure 1 - Serum amylase and lipase concentrations.

Table 1 - Reports of the imaging exams.

D0 *Start point MB PCT*
D28 *First hospitalization*
D28 **TOTAL ABDOMEN CT**: • Signs of acute pancreatitis. Diffuse tail/body thickening with edema. • No signs of dilation of the intra and extrahepatic bile ducts.
D34 **UPPER ABDOMEN MRI AND CHOLANGIORESONANCE**: • Signs of acute pancreatitis, with tail edema. • Gallbladder with finely heterogeneous content, suggesting billiary sludge. • Discrete amount of free liquid in the upper abdomen. • Focus of parenchymal retraction in the lower pole of the left kidney measuring 13 mm. • Small bilateral pleural effusion. • Edema and hyper signal in FLAIR in the myoadipose flap of the abdominal wall suggesting edema.
D35 *Hospital discharge*
D39 **TOTAL ABDOMEN ULTRASOUND:** • Normally distended gallbladder, with regular walls, anechoic and homogeneous content. • Intrahepatic bile ducts and echographically normal choledochus. • Pancreas partially evaluated, especially the tail region.
D49 **TOTAL ABDOMEN CT**: • Pancreas with normal shape, contours, dimensions and attenuations. • No signs of dilation of intra and extrahepatic bile ducts.
D63 *Resume of MB- PCT*
D65 *Second hospitalization*
D68 **TOTAL ABDOMEN CT**: • Pancreas with normal shape, contours, dimensions and attenuations. • No signs of dilation of intra and extrahepatic bile ducts. • Normal gallbladder, with dense content.
D77 **UPPER ABDOMEN AND PELVIC CT**: • Signs of acute edematous pancreatitis, most evident in the tail. • Normally distended gallbladder, thin-walled, with heterogeneous content suggesting biliary sludge. • No signs of dilation of intra and extrahepatic bile ducts. • Small focus of parenchymal retraction in the lower pole of the left kidney measuring 13mm. • Free laminar peri-pancreatic fluid in the caudal and pelvis.
D81 **THORACIC CT** • Small pericardial effusion. • Small left pleural effusion.
D82 *Hospital discharge*
D97 **UPPER ABDOMEN MRI AND CHOLANGIORESONANCE**: • Signs of mild acute pancreatitis, most evident in the tail. • Gallbladder with finely heterogeneous content, suggesting thick bile. • Focus of parenchymal retraction in the lower pole of the left kidney measuring 13 mm.

doses, but there are no published cases of AP associated with monthly administration of rifampicin, as used in this PCT/MB.

Our patient developed abdominal pain three weeks after starting PCT/MB. The first symptoms of dapsone-induced AP occur from three weeks to one year using the drug. All reported cases of dapsone-induced cases were in male patients. AP associated with rifampicin affected both genders, with at least four weeks of medication use[10-13].

The symptoms presented by the patient were similar to the clinical manifestations described in other case reports. Cutaneous symptoms and other systemic disorders were reported as well. In cases associated with Rifampicin, systemic signs and injuries were more common[2,6-13].

Another evidence that Dapsone was the most likely cause of the patient's acute pancreatitis is the dosage of MB-PCT. The doses of Dapsone from this patient's therapy are similar to those found in the literature, unlike Rifampicin, whose dosage was much lower than those reported in the other case reports[2,6-13].

Biliary sludge without findings of cholelithiasis may rarely induce AP as a consequence of biliary microlithiasis. Microscopic analyses of the bile were not performed in this case[14,15].

Table 2 - Case reports of acute pancreatitis associated with the use of dapsone and rifampicin.

Report	Patient	Clinical history	Clinical evolution
Corp and Gigshan[6]	15 years old, male	Weakness, nausea, vomiting, anorexia, fever and rash. On the 3rd week of treatment of acne vulgaris with dapsone.	Biochemical and imaging tests showed the presence of pancreatitis. He was treated, discharged and advised to avoid sulfones.
Jha *et al*.[7]	87 years old, male	He had abdominal pain for 6 h, radiating to the back, associated with nausea and bilious vomiting. Treatment of a herpetiform dermatitis with dapsone for 4 weeks.	Laboratory and imaging tests confirmed acute pancreatitis. He was treated and discharged on the 5th day, interrupting dapsone and cimetidine. Six months later. He had a new, more severe presentation of acute pancreatitis. He was treated and instructed not to use dapsone again.
Das and Jawed[2]	31 years old, male	Abdominal pain and vomiting for 2 days. On the 3rd month of treatment for pemphigus with dapsone.	Acute pancreatitis was diagnosed by laboratory and imaging tests. He was treated and discharged after 1 month of hospitalization.
Navarro-Mingorance *et al*.[8]	3 years and 5 months, male	Abdominal pain and vomiting for 48 hours. He had been treated for linear IgA dermatitis with dapsone for one year.	Diagnosis of acute pancreatitis by laboratory and imaging tests. With dapsone treatment discontinuation, the patient was discharged in 5 days.
Soliman *et al.*[9]	75 years old, male	Intermittent epigastric pain for a few weeks. He had been using dapsone during the last 5 years to treat a herpetiform dermatitis, with a recent dose increase.	Diagnosis of acute pancreatitis by laboratory and imaging tests. After 2 days of hospitalization, dapsone was discontinued, which improved the clinical condition.
Liu *et al*.[10]	57 years old, male	Abdominal pain, fever and diffuse rash. He had been on anti-tuberculosis therapy for 6 weeks.	Acute pancreatitis was the diagnosis. He was treated and discharged and needed a pancreatic enzyme replacement for 6 months.
Paydas *et al.*[11]	50 years old, male	Nausea, vomiting and decreased urine flow. He was treated for brucellosis with tetracycline, rifampicin and streptomycin before admission.	Imaging, laboratory and renal biopsy confirmed acute pancreatitis. He was discharged with atenolol therapy and methylprednisolone. In the first month, the tests improved, but he continued with amylase and high lipase dosage.
Markov *et al*.[12]	26 years old, female	Itching, weight loss, upper abdominal pain, nausea, vomiting and jaundice. Undergoing anti-tuberculosis therapy.	Patient had pancreatitis and a severe cholestatic hepatitis diagnosed by imaging and laboratory tests. After 4 weeks, he was discharged.
Topping *et al*.[13]	42 years old, male	Discomfort, cough, myalgia and reduced urine flow. He had been on anti-tuberculosis therapy for 1 month.	The patient was diagnosed with acute interstitial nephritis and pancreatitis. Use of rifampicin was discontinued and the renal function was restored.

This case presents a temporal evidence, has a known response pattern, and there was a clinical improvement with the interruption of the medication and worsening with the re-exposure to the drug[16]. According to the Naranjo probability scale, this case is a probable drug reaction, with an overall score of 6. There are previous conclusive reports on this reaction, the adverse reaction appeared and reappeared with the administration of the drug, the patient improved when the drug was discontinued and the adverse event was confirmed by an objective evidence. However, this reaction could have happened due to other causes (other than the drug)[17]. Considering the WHO-UMC causality assessment, this case is also a probable adverse drug reaction[18].

Therefore, considering the evidence in the literature and the reported case, it is important to take into account that there is a risk of acute pancreatitis in patients on multidrug therapy for leprosy, especially due to dapsone[1-16]. However, the MB-PCT must not be delayed after the diagnosis of leprosy, even in the absence of screening for these complications.

Therefore, taking into account the evidence in literature and the reported case, dapsone is the most evident etiological cause of AP in this case[1-16].

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