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Case report

Drug-Induced Pancreatitis Due to Deferasirox: A Case Report

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Abstract

Pancreatitis, or inflammation of the pancreas, is a common reason for medical consultation, particularly in emergency departments when patients present with abdominal pain. It represents a significant financial burden on healthcare systems, as one in three cases progresses to moderate or severe pancreatitis, leading to increased morbidity, mortality, and complications. Currently, the primary causes of pancreatitis include obstructive biliary and non-biliary factors, resulting from reflux and the absence of enzyme flow into the intestine. This leads to enzyme activation within the pancreatic tissue, causing self-digestion. Alcohol consumption and hypertriglyceridemia contribute to cellular toxicity due to the metabolic breakdown of these substances. Drug-induced pancreatitis is a rare condition associated with antibiotics, analgesics, and antidepressants. Deferasirox, an iron chelator primarily used in patients requiring frequent blood transfusions to prevent iron overload, has rarely been linked to pancreatitis. However, available data suggest a possible correlation, and the pharmaceutical manufacturer lists pancreatitis as a potential adverse effect in the drug's technical specifications. This report presents the case of a 71-year-old female patient who developed moderate to severe pancreatitis without major complications. Physicians ruled out the most common causes of pancreatitis and concluded that the triggering factor was the iron-chelating agent deferasirox.

Keywords

Pancreatitis, acute pancreatitis, abdominal pain, deferasirox, Exjade.

INTRODUCTION

Inflammation of the pancreas, known as pancreatitis, is a common condition. It is the leading cause of gastrointestinal-related consultations in the United States, resulting in significant morbidity and mortality, as well as increased healthcare costs. This condition accounts for up to 275,000 hospitalizations annually, with an incidence ranging from 13 to 45 cases per 100,000 inhabitants per year in the United States[1,2].

It is important to note that the three abdominal diagnoses associated with the highest healthcare costs are gastrointestinal bleeding, gallbladder disease, and pancreatitis, representing an expenditure of over 12 billion dollars annually. In 2018, pancreatitis accounted for up to 195,000 emergency department visits and 562,000 outpatient visits in the United States, with up to 65.6% of these patients requiring hospitalization, and an average cost per hospitalization of 23,472 dollars per patient[3,4].

In Colombia, the two main etiologies are biliary pancreatitis and alcohol-related pancreatitis. Most cases are mild and follow a satisfactory course; however, up to 30% are moderate to severe cases, with mortality rates rising dramatically from 5% to 35%. In the country, the incidence is 34 cases per 100,000 inhabitants[5,6].

In developed countries, gallstone obstruction has been reported to account for 38% of cases. The mechanism by which pancreatitis develops is related to the lodging of a gallstone in the biliary tract, causing obstruction. This leads to increased ductal pressure and decreased flow, which causes the enzymes produced in the exocrine pancreas to be activated in its interior[7]. Alcohol is considered the second most common cause, although its pathophysiology is not clearly established. Studies have described that alcohol can be partially metabolized by the exocrine pancreas through oxidative and non-oxidative mechanisms. However, during degradation and elimination, the molecule first binds to fatty acids, forming lipophilic fatty acid ethyl esters. These molecules are well tolerated by pancreatic cells at low concentrations; however, when accumulation occurs, they interfere with the calcium gradient required for exocytosis and also cause mitochondrial toxicity by disrupting oxidative phosphorylation, leading to a secondary drop in adenosine triphosphate levels and resulting in cell death[8].

A controversial and rare cause is hypercalcemia. Patients with conditions associated with elevated serum calcium levels may develop pancreatitis, as the deposition of calcium salts is cytotoxic to pancreatic cells. Moreover, the increase in extracellular calcium concentrations enhances the release and subsequent activation of trypsinogen, triggering pancreatic autodigestion[9].

PRESENTATION OF THE CASE

The patient is a 71-year-old woman with a history of myelodysplastic syndrome associated with chronic anemia, requiring transfusion support every 25 days as indicated by the hematology department. She was being treated with deferasirox. She presented with abdominal pain predominantly in the epigastric region, associated with multiple episodes of vomiting with food content. Management with omeprazole, sucralfate, and sodium alginate was initiated; however, the patient did not respond to treatment, and additional studies were performed (**Table 1**).

In this context, a diagnosis of pancreatitis was considered, and additional studies were requested to determine the possible cause. An abdominal ultrasound was performed, which did not reveal any abnormalities; however, the pancreas could not be evaluated due to gas interposition. The report noted a postcholecystectomy status. Magnetic resonance cholangiopancreatography (MRCP) showed an increase in pancreatic size and diffuse signal intensity, with alteration of the adjacent fat. Peripancreatic fluid was observed, extending bilaterally to the anterior pararenal space and toward the paracolic gutters, as well as the perihepatic and perisplenic regions. In addition, ectasia of the extrahepatic bile duct was reported, without evidence of any obstructive cause (**Figure 1**).

Table 1. Laboratory tests

Test	Observed value	Reference value
Amylase	721 U/L	28-100 U/L
Lipase	1539 U/L	13-60 U/L
ALT	103.6 U/L	0-31 U/L
AST	97.8 U/L	0-32 U/L
Total bilirubin	1.41 mg/dL	0-1 mg/dL
Direct bilirubin	0.96 mg/dL	0-0.3 mg/dL
Indirect bilirubin	0.45 mg/dL	
Hemogram		
Hemoglobin	9.1 g/dL	12.3-15.3 g/dL
Leukocytes	13.2 10 3/µL	4.5-11.3 10 3/µL
Platelets	210 10 3/µL	150-450 10 3/µL
Serum calcium	10 mg/dL	8.8-10.2 mg/dL
Triglycerides	88.7 mg/dL	0-150 mg/dL
CRP	5.8 mg/dL	0-5 mg/L

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein. Table created by the authors.

The patient presented clinical and paraclinical findings consistent with pancreatitis. After ruling out the most common causes, a consultation was requested with the gastroenterology department, where it was determined that this was a case of moderately severe pancreatitis. As further studies were carried out to determine the origin, an endoscopic ultrasound was performed, which reported acute pancreatitis without biliary duct dilatation, without lithiasis, with absence of the gallbladder, and a normal papilla.

The patient showed gradual but steady improvement, with increasing tolerance to the initial diet and its progression, along with better control of abdominal pain. Since no typical causes of pancreatitis were found, the patient's medication history was reviewed again. A possible association between the iron chelator and pancreatitis was identified. These reports describe that this association is more frequent in pediatric patients, probably due to the higher incidence of hematologic disorders, although there remains a risk when using deferasirox in adult patients. The hematology team agreed with this etiological approach and discontinued the administration of this drug. The patient

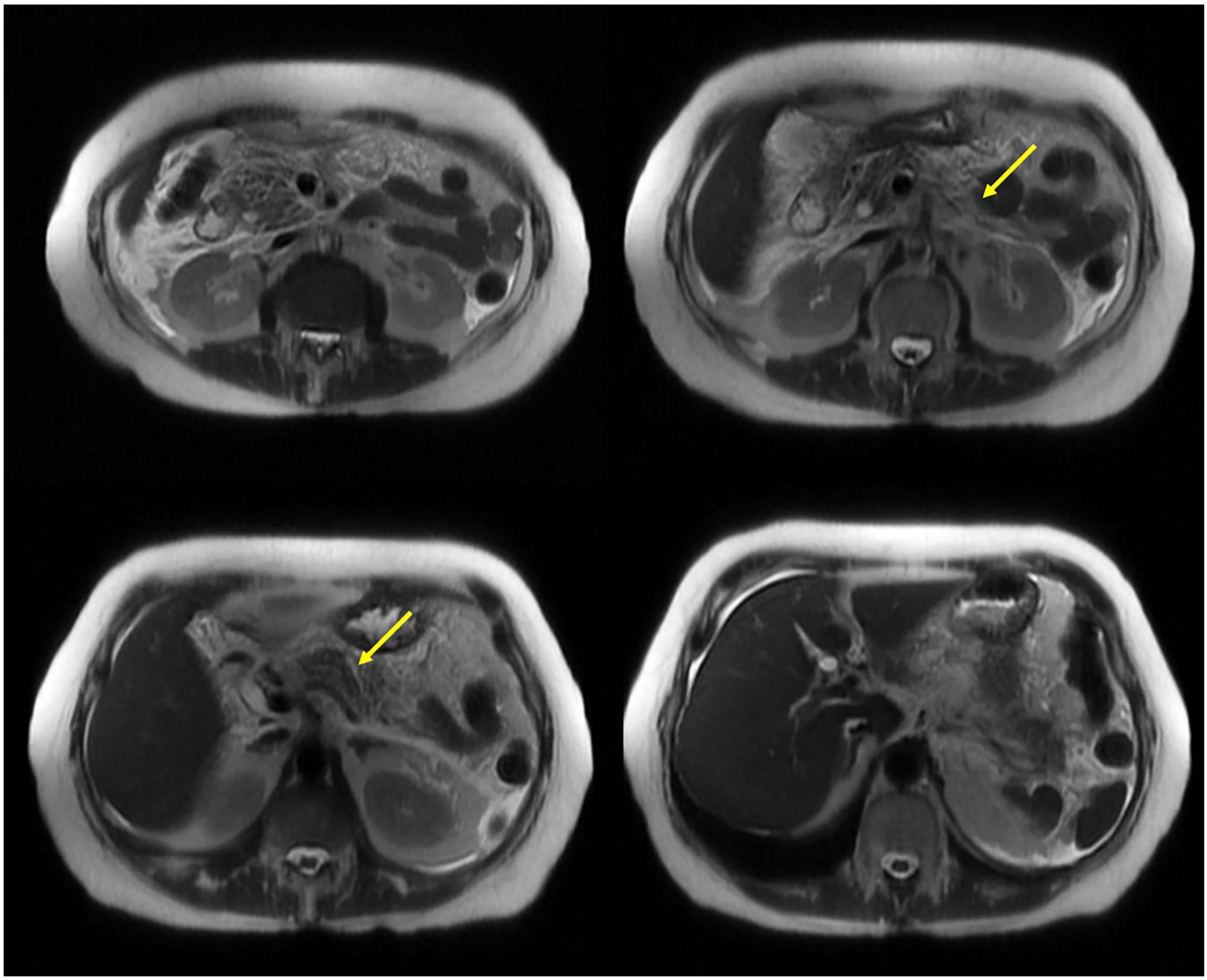

Figure 1. Abdominal MRCP: The pancreas shows a diffuse increase in size and signal intensity, with alteration of the adjacent fat. There is peripancreatic fluid extending bilaterally into the anterior pararenal spaces and along the paracolic gutters, as well as into the perihepatic and perisplenic regions. Images property of the authors.

ultimately had a favorable clinical course, with normalization of biochemical parameters, and was discharged from the hospital. The next step is to assess whether the patient will require reinitiation of an iron chelator due to the frequent and multiple transfusions, while considering the risk of recurrent pancreatitis.

DISCUSSION

Deferasirox is an iron-chelating drug developed by Novartis and approved by the U.S. Food and Drug Administration (FDA) in 2005 for the management of iron overload, a common condition in patients requiring frequent blood transfusions due to various pathologies[10]. It works by forming irreversible bonds with ferric iron in a 1:1 ratio, leading to the subsequent fecal elimination of the formed complex, thereby removing the excess iron. It is important to mention that there are no endogenous systems that respond to the increase in iron levels, there are only mechanisms to store it[11].

The first study demonstrating its efficacy was published in *The Lancet* in 2003, which included patients with β-thalassemia requiring frequent transfusion support. The results showed that, compared to a placebo, it reduced iron

levels and also had an appropriate safety profile[12]. Later, in 2006, a study was published in the journal *Blood* that included patients with β-thalassemia and compared deferasirox with deferoxamine in terms of reducing hepatic iron concentration. This study demonstrated slightly greater effectiveness, though not statistically significant; however, deferasirox is an oral agent, which, compared to slow infusion or subcutaneous administration, also showed an appropriate safety profile. Gastrointestinal symptoms were common but self-limited in less than eight days. The administration of these drugs also resulted in a mild elevation of transaminases in most patients, and in two cases, treatment was discontinued due to drug-induced hepatitis[13].

In the randomized studies, pancreatitis related to deferasirox was never mentioned. However, there is a follow-up study in which one case of acute pancreatitis was reported as an adverse effect[14]. In 2015, the Health Sciences Authority (HSA) issued an alert describing a review of VigiBase, the World Health Organization's (WHO) database, which identified 14 possible cases of pancreatitis related to this drug. In three of these cases, confusion with other medications could have occurred. However, in the remaining 11 cases, deferasirox was the only drug associated, prompting the company to investigate the correlation. Health professionals were advised to exercise caution when using the drug and consider the potential risk, even though it is a rare event[15,16]. In 2021, Novartis developed a manual for patients using deferasirox that includes pancreatitis as a possible adverse effect of this agent[17], and various monitoring entities included this potential adverse effect in the medication's precautions[18,19].

In the presented case, the patient was definitively diagnosed with pancreatitis based on the clinical presentation, laboratory results, and imaging. She was managed by a multidisciplinary team, including specialists in internal medicine, gastroenterology, and hematology. The primary causes of pancreatitis were objectively ruled out, and the treating team, based on evidence and clinical experience, determined it to be a case of drug-induced pancreatitis caused by deferasirox.

CONCLUSIONS

Drug-induced pancreatitis can be a challenging diagnosis, especially in the case of iron chelators, given their limited use and relative infrequency. It is important not to overlook common causes and to subsequently individualize the diagnosis for each patient. In these cases, having a multidisciplinary team of experts is crucial to offer the best approach and management for each patient. This report does not aim to discourage the use of the drug in question, but rather to inform the scientific community about the existence of this potential condition.

Conflicts of interest and ethical issues

Informed consent was obtained from the participant in this case report. This research is based on medical records, and there was no direct contact or intervention with the patients; all data collection was conducted by researchers based on the medical records. No patient was at risk due to the interventions.

All behaviors and actions carried out by the researchers are in accordance with the Belmont Report. All data were collected and analyzed in an appropriate and transparent manner with the active participation of the corresponding author and certified in good clinical practices by the NIDA clinical trial networks.

The researchers openly declare that they have no financial support of any kind, and this research project is purely academic. Due to the methods of this study, no budget was necessary, and the members of the research team declare their absolute commitment to the collection and analysis of data without any financial interests.

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Pancreatitis medicamentosa por deferasirox: reporte de un caso

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