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ACUTE DRUG-INDUCED PANCREATITIS SECONDARY TO AZATHIOPRINE: A CASE REPORT AT THE PEDIATRIC DEPARTMENT OF RABAT MILITARY HOSPITAL

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ABSTRACT

Azathioprine (Imurel) is commonly used in the treatment of autoimmune diseases, including autoimmune hepatitis. Although generally well tolerated, azathioprine can occasionally induce serious adverse effects, such as acute pancreatitis. We report the case of a 12-year-old girl with autoimmune hepatitis treated with azathioprine 2 mg/kg/day and corticosteroids 2 mg/kg/day. Two weeks after the introduction of azathioprine, the patient was admitted to hospital with severe abdominal pain and apyrexia. Clinical examination revealed epigastric tenderness with no other significant abnormalities. Biological investigations revealed hyperlipaemia at 295 IU/L, elevated liver enzymes and cytopenia. Abdominal ultrasound and computed tomography (CT) confirmed the diagnosis of acute pancreatitis (stage IB) associated with portal hypertension and splenomegaly with ascites. Treatment consisted of azathioprine discontinuation, digestive rest and analgesic therapy. The clinical course was favorable, with disappearance of abdominal pain and normalization of lipasemia. This case illustrates the importance of closely monitoring patients on azathioprine for signs of acute pancreatitis, and of acting promptly in case of suspicion.

KEYWORDS: Acute pancreatitis, Azathioprine, Autoimmune hepatitis, Child, Side effects.

INTRODUCTION

Azathioprine (Imurel) is an essential immunosuppressant in the treatment of autoimmune hepatitis (AIH). This chronic condition often requires long-term immunosuppression to prevent relapses and maintain lasting remission. Thanks to its efficacy and relatively favorable safety profile, azathioprine is commonly used in combination with corticosteroids, or as monotherapy once the disease has stabilized.

The side effects of azathioprine can be divided into two categories: those that are dose-dependent, such as myelotoxicity and hepatotoxicity, and those that are dose-independent, including allergic reactions such as fever, rash, arthralgia and, more rarely, acute pancreatitis (AP). Although rare, drug-induced pancreatitis is a severe complication requiring prompt recognition and appropriate management.

We present here the case of a 12-year-old girl, followed for autoimmune hepatitis and treated with azathioprine at a dose of 2 mg/kg. Two weeks after the introduction of Imurel, the patient was admitted with severe abdominal pain in the context of apyrexia. This clinical presentation led to the diagnosis of acute pancreatitis secondary to azathioprine.

PATIENT AND OBSERVATION

A 12-year-old girl with autoimmune hepatitis was treated with azathioprine (Imurel) at a dose of 2 mg/kg/day and corticosteroids at a dose of 2 mg/kg/day. Two weeks after the introduction of Imurel, the patient was admitted to hospital with severe epigastric abdominal pain and apyrexia.

On admission, the patient was conscious, anicteric, apyretic and hemodynamically stable. Abdominal examination revealed a distended, soft abdomen with epigastric tenderness to palpation. The rest of the physical examination was unremarkable.

Paraclinical examinations revealed the following results: haemoglobin 11 g/dL, white blood cells (WBC) 2.2 G/L, neutrophils (NNP) 1.6 G/L, and platelets (PLQ) 67 G/L. The blood ionogram showed no hydroelectrolytic disturbance, and the CRP was negative. Renal function

tests were normal. Liver function tests showed ALT at 118 IU/L, ASAT at 86 IU/L, GGT at 394 IU/L, alkaline phosphatase (ALP) at 241 IU/L, prothrombin level (PT) at 55%, fibrinogen at 1.5 g/L and factor V at 71%. Hyperlipaemia was noted at 295 IU/L.

Abdominal ultrasound revealed portal hypertension with ascitic decompensation. Abdominal computed tomography (CT) showed stage IB pancreatitis with a swollen pancreas without necrosis or casting, associated with adenopathy, and portal hypertension with splenomegaly and copious ascites.

Therapeutically, the patient was put on digestive rest and analgesic treatment. Azathioprine was discontinued on suspicion of immunoallergic pancreatitis. Corticosteroid therapy was gradually reduced. Clinico-biological evolution was favorable, with disappearance of abdominal pain and normalization of lipasemia, which was 23 IU/L at follow-up.

DISCUSSION

Acute pancreatitis typically manifests as acute pain in the upper abdomen, often in the epigastrium, frequently radiating to the back. The onset of pain can be rapid, peaking within 30 minutes, and often persisting for more than 24 hours without analgesia. Associated symptoms such as nausea and vomiting are also common. To confirm the diagnosis of acute pancreatitis, it is essential to consider biochemical (serum amylase or lipase), radiological and sometimes histological evidence.[1,2]

Drug-induced pancreatitis accounts for 0.1% to 2% of cases. Several drugs are known to induce this condition, including azathioprine (AZA), L-asparaginase, thiazide diuretics, estrogens, tamoxifen, valproic acid, and others. Risk factors for drug-induced pancreatitis include age, with increased risk in children, female gender, and immunocompromised patients.[3,4]

The diagnosis of drug-induced pancreatitis is often complex due to the absence of typical symptoms and specific biochemical and radiological features. It is usually established when the patient is taking a drug known to induce acute pancreatitis and in the absence of other identifiable causes. The reappearance of symptoms after re-administration of the suspected drug reinforces the causal link.[3]

Badalov and colleagues have classified drugs according to the level of evidence reported for acute pancreatitis, establishing four classes ranging from the most likely (class I) to the least likely (class IV). Azathioprine belongs to class I, indicating a high probability of causality. Nitsche et al. also established a causal link between acute pancreatitis and a list of 31 drugs, with azathioprine among the most frequently implicated. In addition, azathioprine is one of more than 500 drugs suspected of inducing pancreatitis, according to the WHO database established in 1968.[5]

A number of studies have evaluated the association between the adverse effects of azathioprine and genetic polymorphism of the genes coding for the thiopurine methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (ITPase) enzymes involved in its metabolism. Only one study has demonstrated a significant association between increased pancreatitis and mutation of an allele of the gene coding for ITPase.[6,7]

In terms of management, immediate discontinuation of the suspected molecule is crucial. General care should be instituted, including restoration of blood volume with adequate fluid intake to avoid tissue hypoxia secondary to hypovolemia, and oxygen supplementation during the first 48 hours may be necessary. Frequent monitoring of vital signs and oxygen saturation is important, especially when narcotics are used for pain control. Metabolic and electrolyte disorders (hyperglycemia, hypertriglyceridemia, hypocalcemia, hypomagnesemia) should be corrected.

Symptomatic treatment of abdominal pain with parenteral narcotic analgesics is often required. In terms of nutrition, recent changes recommend that in cases of mild acute pancreatitis, enteral nutrition should be preferred to total parenteral nutrition, thus reducing complications and costs.[1] When oral intake is resumed, a low-fat diet is generally introduced.

In our case, the patient presented with acute pancreatitis, probably induced by azathioprine, introduced for the treatment of autoimmune hepatitis. Discontinuation of azathioprine led to rapid and significant clinical improvement, with normalization of lipemia and disappearance of abdominal pain. This observation underlines the importance of clinical vigilance and close monitoring when using azathioprine, particularly in children, due to the potentially severe risk of acute pancreatitis.

LES REFERENCES

1. Banks Pa, Freeman mL. Practice Parameters Committee of the American College of Gastroenterology. Practice Guidelines in acute pancreatitis. Am j Gastroenterol., 2006; 101(10): 2379-400.
2. Forsmark ce, baillie J. AGA institute Clinical Practice and economics Committee; AGA institute Governing Board. AGA institute technical review on acute pancreatitis. Gastroenterology, 2007; 132(5): 2022-44.
3. Balani ar, Grendell Jh. Drug-induced pancreatitis: incidence, management and prevention. Drug Saf., 2008; 31(10): 823-37.
4. Nitsche cJ, Jamieson N, Lerch mm, et coll. Drug induced pancreatitis. Best Pract Res Clin Gastroenterol., 2010; 24(2): 143-55.
5. Badalov N, baradarian r, iswara K, et col**l.** Drug-induced acute pancreatitis: An evidence-based

review. Clin Gastroenterol Hepatol, 2007; 5(6): 648-61.
6. De ridder L, Van Dieren Jm, Van Deventer hJ, et coll. Pharmacogenetics of thio- purine therapy in paediatric iBD patients. Aliment Pharmacol Ther., 2006; 23(8): 1137-41.
7. marinaki am, ansari a, Duley Ja, et coll. Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphos- phate pyrophosphatase (iTPase). Pharmacogenetics., 2004; 14(3): 181-7.