Azathioprine-induced acute pancreatitis in inflammatory bowel disease : natural history and severity spectrum

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To the Editor,

Crohn's disease (CD) and ulcerative colitis (UC) may present with various extra-intestinal manifestations, including acute pancreatitis (AP) (1). Recent studies estimate that up to 7% of patients with CD treated with azathioprine develop acute pancreatitis, which is not dose-dependent and generally occurs 4 to 6 weeks after the beginning of the drug (2). However the pathogenic mechanism is unknown (3).

Our aim was to characterize the population of patients who developed azathioprine-induced AP in a tertiary referral center with a large number of treated IBD patients. For that, we retrospectively identified all patients with IBD admitted to our Gastroenterology department for azathioprine-induced AP between January 2006 and December 2015.

The diagnosis of acute pancreatitis was made by the presence of at least two of the following criteria: acute epigastric pain, elevated serum amylase and/or lipase (at least 3 times the normal range) and/or characteristic features in imaging exams. The diagnosis of acute pancreatitis induced by azathioprine was carried out according to the temporal relationship between onset of symptoms and start of therapy or dose adjustment. In all cases the medical history of patients was reviewed, including history of excessive alcohol consumption, and was excluded biliary cause for pancreatitis.

The severity of the acute pancreatitis was established according to the BISAP score (4).

In our cohort, the prevalence of acute pancreatitis was 3.5% (571 patients on azathioprine). The condition was diagnosed in 20 patients, with no differences between genders, and all of them had CD. Table 1 shows the baseline characteristics of the study population.

Table 2 shows the characteristics of cases of acute pancreatitis induced by azathioprine in our department. The median duration of azathioprine therapy was 21 days (IQR: 15-30 days), with a median dosage of 63 mg/Kg/day (IQR: 50-100 mg/Kg/day). Four patients (20%) had their dose increased in the week before. No patient showed other azathioprine-related side effects. No patient was on biologic therapy. All patients presented with mild disease, with BISAP scores ≤2. Abdominal pain was the main symptom at diagnosis (present in 95% of cases), often accompanied by vomiting (35%) and low grade fever (25%). One patient had previous history of pancreatitis, of unknown etiology. Just 16% of patients revealed pancreatic edema in abdominal ultrasound. The median hospital stay was 7 days (IQR: 3-9 days). All patients improved after discontinuation of azathioprine, and no patient was re-challenged with 6-mercatopurine.

Azathioprine is an established risk factor for acute pancreatitis in IBD. As in other series5, a presumptive diagnosis was made since it was found that azathioprine had been started recently, establishing a temporal relationship between the onset of clinical manifestations and this drug. Furthermore, since all cases resolved within a few days after cessation of azathioprine it reinforces the diagnosis. As such, other etiologies, including pancreatitis induced by mesalazine were excluded.

Acute pancreatitis induced by azathioprine is usually mild in severity. Only CD appears to have predictive factor of acute pancreatitis, but the reason for that remains unknown. In particular, active smoking seems to predispose to this entity, as 35% of our patients were active smokers, which meets with newly published data2.

Concomitant corticosteroid therapy has not proven to be a protective factor. All patients receiving steroids were treated with oral prednisolone, and none with budesonide, however, the dose of corticosteroids may be an important factor and future studies may answer this question.

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Table 1. — Summary of patient´s demographics

	n = 20
Male/Female	10/10
Age at diagnosis of pancreatitis (median)	32 years (IQR: 22-42 years)
Age at diagnosis of IBD (median)	26 years (IQR: 21-39 years)
Harvey-Bradshaw index (median)	2 (IQR: 0-6)
Extra-intestinal manifestations (%)	2 (10%)
Previous surgery	2 (10%)
Smoking habits (%)	
Active	7 (35%)
Former	1 (5%)
No	12 (60%)
Alcoholic intake	
Yes	2 (10%)
No	18 (90%)
Montreal classification	
Age (%)	
A2	17 (85%)
A3	3 (15%)
Localization (%)	
L1	9 (45%)
L2	1 (5%)
L3	6 (30%)
L1-L4	3 (15%)
L3-L4	1 (5%)
Phenotype (%)	
B1	16 (80%)
B2	2 (10%)
B3	2 (10%)
Perianal disease (%)	5 (25%)

Table 2. – Azathioprine-induced pancreatitis characteristics

	n = 20
Median dose of azathioprine (mg/Kg/day)	63 (IQR: 50-100)
Time since onset of azathioprine (days)	21 (IQR: 15-30)
Recent dose adjust (days)	20 (4 – 90)
Symptoms (%)	
Abdominal pain	8 (40%)
Abdominal pain + vomiting	6 (30%)
Abdominal pain + fever	4 (20%)
Abdominal pain + fever + vomiting	1 (5%)
Fever + vomiting	1 (5%)
Severity (%)	
Mild	15 (100%)
Concomitant treatment (%)	
No	8 (40%)
Steroids	6 (30%)
Messalazine	4 (20%)
Antibiotics	2 (10%)
Laboratorial findings (median)	
Amilase (U/L)	142 (IQR: 99-296)
Lipase (U/L)	388 (IQR: 226-768)
AST (U/L)	20 (IQR: 15-55)
ALT (U/L)	18 (IQR: 13-71)
GGT (U/L)	36 (IQR: 18-94)
FA (U/L)	78 (IQR: 61-91)
Total bilirubin (mg/dL)	0.55 (IQR: 0.4-0.97)
White blood count ($x10^9$)	13.8 (IQR: 10.48-18.12)
C-reactive protein (mg/L)	78.65 (IQR: 45.5-144.8)
LDH (U/L)	187 (IQR: 147-277)

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