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Association between autoimmune pancreatitis and ulcerative colitis: a report of 12 patients

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ABSTRACT

Introduction: pancreatic manifestations in inflammatory bowel disease (IBD) mainly include acute pancreatitis secondary to drugs and, less frequently, autoimmune pancreatitis, in particular type 2 autoimmune pancreatitis**.**

Methods: retrospective study of patients diagnosed with ulcerative colitis (UC) and autoimmune pancreatitis (AIP) in control at two centers in Santiago, Chile, between 2007 and 2018. Clinical data, laboratory results, images and response to treatment were recorded.

Results: twelve patients were identified with both diseases, the average age was 34 years and 42 % were male. In all cases, a likely diagnosis with type-2 AIP was established based on pancreatic magnetic resonance imaging (MRI), association with IBD and a rapid response

to therapy with corticosteroids. Samples for histology were obtained from two patients, which showed inconclusive results. AIP recurrence was reported in only one case. A total of 58 % of patients had extensive UC, 100 % received 5-ASA therapy and 33 % were treated with azathioprine. Only one patient had a serious flare-up, none developed complications and none required biologics or surgery.

Conclusion: an association between UC and type-2 AIP was confirmed in our cases. No increase in IBD severity was observed in this group of patients.

Keywords: Inflammatory bowel disease. Ulcerative colitis. Pancreatitis. Autoimmune pancreatitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition of the gut that encompasses two disorders: ulcerative colitis (UC) and Crohn's disease (CD). It is characterized by inflammatory activity in any segment of the gastrointestinal (GI) tract, from the mouth to anus in the case of CD, and by colonic involvement in the case of UC, with activity and remission phases. Up to 35-40 % of patients exhibit extraintestinal manifestations, primarily in the joints, skin and eyes. Pancreatic involvement may be seen in IBD due to medication-related adverse events. This includes acute pancreatitis related to azathioprine (AZA) or mesalazine, or in association with other autoimmune diseases such as autoimmune pancreatitis (AIP) type 2 (1-7).

AIP was identified in 1961 and two subtypes were described in 2003: lymphoplasmacytic sclerosing pancreatitis (AIP type 1) and idiopathic duct-centric pancreatitis (AIP type 2). The former is an IgG4-related condition that mostly affects men older than 50 years. Peripheral blood IgG4 levels are elevated in 50-75 % of cases and the condition may involve several organs. AIP type 2 (AIP-2) affects patients aged 30 to 40 years and both genders are equally affected. IgG4 levels are nearly always normal and there is an association with IBD (8-15). AIP-2 is more commonly associated with UC than with CD, as demonstrated by the studies

of Hart et al. and Ueki et al., where only 16 % (3/19) and 29 % (2/7) of patients with AIP-2 were diagnosed with CD, respectively (11,16,17).

Figure 1 shows the 2011 International Consensus Diagnostic Criteria for AIP-2 (16). Unfortunately, this AIP type has no serological diagnosis; even though various autoantibodies may be present, none have shown an acceptable specificity and sensitivity (17). Diagnosis is based on magnetic resonance imaging (MRI) in the clinical practice, which reveals diffuse or focal enlargement of the pancreatic parenchyma with delayed contrast enhancement. This may occur with a peripancreatic halo, giving the pancreas a sausage-like appearance. Magnetic resonance cholangio-pancreatography (MRCP) also reveals main-duct strictures, with or without subsequent Wirsung duct dilatation. The incidence of UC in patients with AIP-2 may be up to 35 %. However, the incidence of AIP-2 in patients with UC is low. The prevalence of AIP in UC has been estimated at 0.54 % (18). The impact of the association of these two conditions remains unclear. In fact, some publications report a higher UC severity and greater colectomy risk, whereas other studies did not show any differences in UC extent or severity among patients with AIP-2 (3,12,18). Here we report our experience in patients with both IBD and AIP with the aim of drawing attention to this association, which, although uncommon, is of clinical significance. The goal of this study was to assess the clinical association between AIP-2 and UC and to describe the clinical presentation of both conditions, their imaging characteristics and their response to treatment. A secondary endpoint was to assess the severity of UC in patients with AIP-2.

METHODS

A retrospective, descriptive study was performed of all patients diagnosed with AIP and UC being monitored at two hospitals in Santiago de Chile from 2007 to 2018. Both centers are reference sites in the study and management of patients with pancreatic disease in Chile, due to the experience of one of the authors in this subject matter. All patients with an established diagnosis of AIP followed up in either center were included in the study. Pancreatitis cases with a different etiology were excluded. The diagnosis of AIP was based

on clinical manifestations, serology, imaging techniques and response to treatment. The diagnosis of UC was based on the clinical picture, colonoscopy findings and biopsy results. None of the AIP patients had CD, hence this condition was not included in the data analysis. Furthermore, there was no association of IBD with type-1 AIP among our patients.

Patients were identified using personal recordings obtained by one author over time. The clinical records were retrospectively reviewed, once the study was approved by the Ethics Committee at Hospital Clínico Universidad de Chile. Demographic data, comorbidities, lab testing results and diagnostic images were collected for all patients diagnosed with AIP and UC.

RESULTS

Twelve patients with a diagnosis of AIP and UC under follow-up at the Hospital Clínico Universidad de Chile and/or Clínica Dávila between 2007 and 2018 were identified. The mean age was 34 years (range 26-46) at the time of analysis, 28 years (range 19-40) at the time of diagnosis with AIP, 29.2 years (range 19-45) at the time of diagnosis with UC and 42 % were male. AIP and UC were synchronously diagnosed in four patients (33 %) and AIP was diagnosed before UC in five cases. Table 1 shows the clinical and demographic characteristics of this group of patients.

AIP course

The most common AIP presentation in this group of patients was acute pancreatitis (AP, 83 %), i.e., abdominal pain accompanied by elevated pancreatic enzymes. Amylase or lipase levels were significantly high in the blood of six patients, with increases of < 3-fold in three additional individuals with compatible diagnostic images. This included one case that previously underwent surgery and pancreatic remnant images were initially interpreted as AP. Obstructive jaundice was the predominant symptom in one patient and two subjects had mild jaundice. AP presentation was always mild without local or systemic complications but with a slow recovery and persistent pain that subsided very rapidly when prednisone

was initiated. IgG4 levels were normal in all patients and peripheral eosinophilia was reported in two cases.

A diagnosis was established based on clinical and imaging findings. Other potential etiologic factors were ruled out in all subjects. Two patients received azathioprine before AIP onset for UC. However, AIP responded to therapy and AZA discontinuation was not required with no subsequent relapse. Seven patients underwent abdominal computed tomography (CT) scans and characteristic AIP findings were seen in two subjects. Diffuse pancreatic enlargement without necrosis or peripancreatic fluid was seen in the remaining five cases, which was consistent with AIP but did not allow other etiologies to be excluded. Pancreatic MRI scans were performed in all 12 patients and all had findings suggestive of AIP. Two patients underwent endoscopic ultrasound (EUS) scans and both had findings suggestive of AIP. One of these subjects underwent a fine-needle puncture but the results were inconclusive, as was a biopsy obtained from the papilla of Vater in another patient. Two patients underwent a pancreatography, which revealed multiple narrowings in the main pancreatic duct in both cases. One patient had a history of a pancreatoduodenectomy 19 years previously for suspected pancreatic cancer, which was ruled out by histology. Unfortunately, the surgical specimens were no longer available for review. We deem it highly likely that the patient originally suffered from type-2 AIP.

All patients received treatment with prednisone at an initial dose of 30-40 mg/day followed by gradual tapering for a total of 3-4 months. The one patient with obstructive jaundice responded rapidly to steroids and the jaundice subsided after one week of treatment with no need for biliary stenting. Complete morphological recovery was documented using a pancreatic MRI scan.

Only one patient had recurrent AIP at the pancreatic remnant 19 years after the pancreatoduodenectomy and responded to prednisone therapy with a complete recovery. Excluding this patient, the average follow-up was 5.4 years (range 1-10). No recurrences were observed in the other subjects. The AIP characteristics in this group of patients are shown in table 2.

UC course

Regarding UC extent, 58 % of cases had pancolitis or extensive colitis. All 12 patients received 5-amino salicylates (5-ASA) as well as corticosteroids during the acute phase. Azathioprine was given to four patients. One patient had a serious flare-up during the study period and responded positively to corticosteroids and then to maintenance azathioprine. Another patient had an infection with *Clostridium difficile* and then recovered satisfactorily. The remaining patients had a favorable clinical outcome with the therapy used. None required therapy with biologics or surgery. No extraintestinal manifestations were reported. The clinical characteristics of UC in this group of patients are shown in table 3**.**

DISCUSSION

The association of UC with pancreatitis is not exceptional. The first possibility that should always be considered is drug-induced pancreatitis. A drug widely accepted as a cause of acute pancreatitis is AZA. In UC, AZA is considered as a major cause of pancreatitis, with a reported rate of 3-7 % within the first few months of treatment onset (1-5,19,20). Four patients in our study received AZA; one had pancreatitis concurrently with treatment onset and one had pancreatitis one year after AZA therapy onset. Both cases were diagnosed with AIP and the drug was maintained with no associated adverse events. Pancreatitis occurred before AZA therapy in the remaining two subjects.

The clinical characteristics of our group of patients are consistent with the international literature: young subjects, no gender-related differences, normal IgG4 levels, AIP diagnosis based on characteristic images, association with UC and a rapid response to treatment with corticosteroids (21-24).

With regard to diagnostic images, pancreatic MRI is considered to be the imaging technique of choice. Hallmark findings in AIP include diffuse pancreatic parenchyma enlargement with delayed enhancement. The gland increases in size and loses its lobular structure, thus acquiring a “sausage-like” appearance. Other findings suggestive of AIP include the

presence of a halo around the pancreas and a long stricture of the main pancreatic duct or multiple segmentary stenoses. In the case of a focal involvement, a mass may be seen at the head or body, which requires a differential diagnosis from pancreatic adenocarcinoma (10-13,25,26).

Following therapy with corticosteroids, the parenchyma affected by AIP diminishes in size, vascularization returns to normal and main pancreatic duct strictures resolve. All of which are considered as a part of the diagnostic criteria of the condition (16,22,24). In our study, all patients had typical MRI findings and the pancreas returned to normal in all 12 subjects after treatment with corticosteroids.

The International Consensus Diagnostic Criteria for AIP defines the need for a histological assessment in order to establish a definitive diagnosis of AIP-2 (Fig. 1). A histological diagnosis is made with pancreatic tissue obtained by surgical resection or EUS-guided biopsy. The usefulness of EUS-guided fine-needle puncturing is controversial as inadequate samples are commonplace. However, recent studies show a yield approaching 60 % when in expert hands (16,27,28).

A limitation of our study was the absence of histological confirmation of AIP-2. In the sole biopsied case, the cytology results were inconclusive. Technological developments and the availability of newer EUS needles have significantly improved pancreatic biopsy yield and histological ascertainment will hopefully be obtained for future cases (29,30). In the absence of a histological diagnosis, the association with IBD is relevant for AIP classification. AIP diagnosis is ascertained via imaging tests and response to treatment with steroids. An association with IBD and normal IgG4 levels greatly support AIP classification as type 2 (Fig. 1). A definitive diagnosis with type-2 AIP is only possible with a histological assessment, which should provide the hallmark finding, namely granulocytic epithelial lesions (GEL) in pancreatic ducts. Even with a biopsy, the histological study may be compatible but inconclusive in the absence of this lesion. Without a biopsy, only a very likely, albeit never definitive diagnosis may be reached. However, in specific cases, insisting on a biopsy

involves ethical aspects, which also has a limited yield as well as potential risks. A rapid and complete response to prednisone sufficiently supports a diagnosis with AIP.

With regard to clinical outcome, this was favorable in all patients. Morphological recovery and a return to normal of pancreatic exocrine and endocrine function was obtained without any sequelae. AIP recurred in only one patient after almost two decades.

Some studies describe a more aggressive course of UC in the presence of AIP, with more severe flares, a need for biologics and a higher rate of colectomies (3,12,18). While the number of subjects in our group was small, which limits the conclusions that can be drawn, we did not observe such aggressiveness. Only one patient had a clinically severe flare-up, none had extraintestinal manifestations, complications or a need for biologics. We made no comparisons to a control group of patients with UC without AIP, but the severity we found was not higher than usual.

The association of these two conditions allows a more likely categorization as AIP-2, but its pathophysiology remains unknown. Ku et al. reported the expression of interleukin 8 (IL-8) in the epithelium of ducts affected by AIP-2. This chemotactic molecule may play a significant role in the pathological mechanism whereby GELs develop (a pathognomonic for AIP-2). Furthermore, a similar expression of IL-8 was seen in the crypt epithelium in biopsy samples obtained by endoscopy for active UC, particularly in cryptitis and cryptic abscesses. Hence, this molecule might be a key factor in the association of UC and AIP-2 (3,31). Along the same lines, expression of an immunomodulating protein, epithelial indoleamine 2,3-dioxygenase (IDO1), has been reported in the duct epithelium of AIP-2 patients as well as in 19 of 25 cases with associated UC (32).

To conclude, while somewhat limited by a low number of subjects and the absence of pancreatic histology, our experience allows us to highlight the clinical significance of the IBD-AIP association. AIP clinical characteristics and course are consistent with the literature. According to our data, there is no association with Crohn's disease nor a more aggressive course of UC in our study.

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Table 1. Clinical and demographic characteristics of 12 patients diagnosed with ulcerative colitis and autoimmune pancreatitis type 2

Clinical and demographic characteristics	
Average age (years)	34 (26-45)
Sex	
Male (n, %)	5 (42 %)
Female (n, %)	7 (58 %)
Smokers (n, %)	3 (25 %)
Alcohol use > 30 g/day	4 (33.3 %)
Diagnosis	
Synchronous	4 (33.3 %)
AIP before UC	5 (41.6 %)
UC before AIP	3 (25 %)
Laboratory (average)	
Lipase U/l	1,456 (normal, 23-300 U/l)
Amylase U/l	152 (normal, 30-110 U/l)
IgG4 mg/dl	41 (normal, 1-135 mg/dl)
Eosinophil count	387 (normal < 500 cells per microliter)

Table 2. Clinical, serological and imaging characteristics of 12 patients with autoimmune pancreatitis (AIP) type 2

Patient	*Sex*	*UC extent*	*AIP clinical presentation*	*IgG4*	*Pancreatic MRI*	*Biopsy*	*Corticoid therapy*	*Recurrence*	*Follow-up (years)*
1	M	Proctosigmoiditis	Jaundice	Normal	Pancreatic head inflammation	Fine-needle puncturing (inconclusive)	Yes	No	7
2	M	Pancolitis	Acute pancreatitis	Normal	Multiple Wirsung strictures		Yes	No	6
3	F	Proctosigmoiditis	Acute pancreatitis	Normal	Diffuse pancreatic inflammation		Yes	No	5
4	M	Pancolitis	Abdominal pain	Normal	Head inflammation and Wirsung strictures	Papilla of Vater (inconclusive)	Yes	No	10
5	F	Pancolitis	Acute pancreatitis	Normal	Pancreatic tail and uncinate process inflammation		Yes	No	4
6	F	Pancolitis	Acute pancreatitis	Normal	Diffuse pancreatic inflammation		Yes	No	10

7	F	Pancolitis	Acute pancreatitis	Normal	Pancreatic tail inflammation		Yes	No	3
8	M	Pancolitis	Acute pancreatitis	Normal	Diffuse pancreatic inflammation		Yes	No	1
9	F	Proctitis	Acute pancreatitis	Normal	Diffuse inflammation and Wirsung strictures		Yes	No	1
10	M	Proctitis	Acute pancreatitis	Normal	Pancreatic remnant inflammation (prior surgery)		Yes	Yes	20
11	F	Pancolitis	Acute pancreatitis	Normal	Diffuse pancreatic inflammation		Yes	No	2
12	F	Proctitis	Acute pancreatitis	Normal	Diffuse pancreatic inflammation		Yes	No	3

Table 3. Clinical characteristics of ulcerative colitis (UC) in 12 patients with autoimmune pancreatitis type 2

Clinical characteristics of UC in patients with AIP-2	
Age at diagnosis with UC (years)	31 (19-43)
Extent (n, %)	
Pancolitis or extensive UC	7 (58.3 %)
Proctosigmoiditis	2 (16.7 %)
Proctitis	3 (25 %)
Clinical severity	Mild-Moderate
Treatment (n, %)	
Corticosteroids	12 (100 %)
5-ASA	12 (100 %)
Azathioprine	4 (33 %)
Biologics	0
Surgery	0

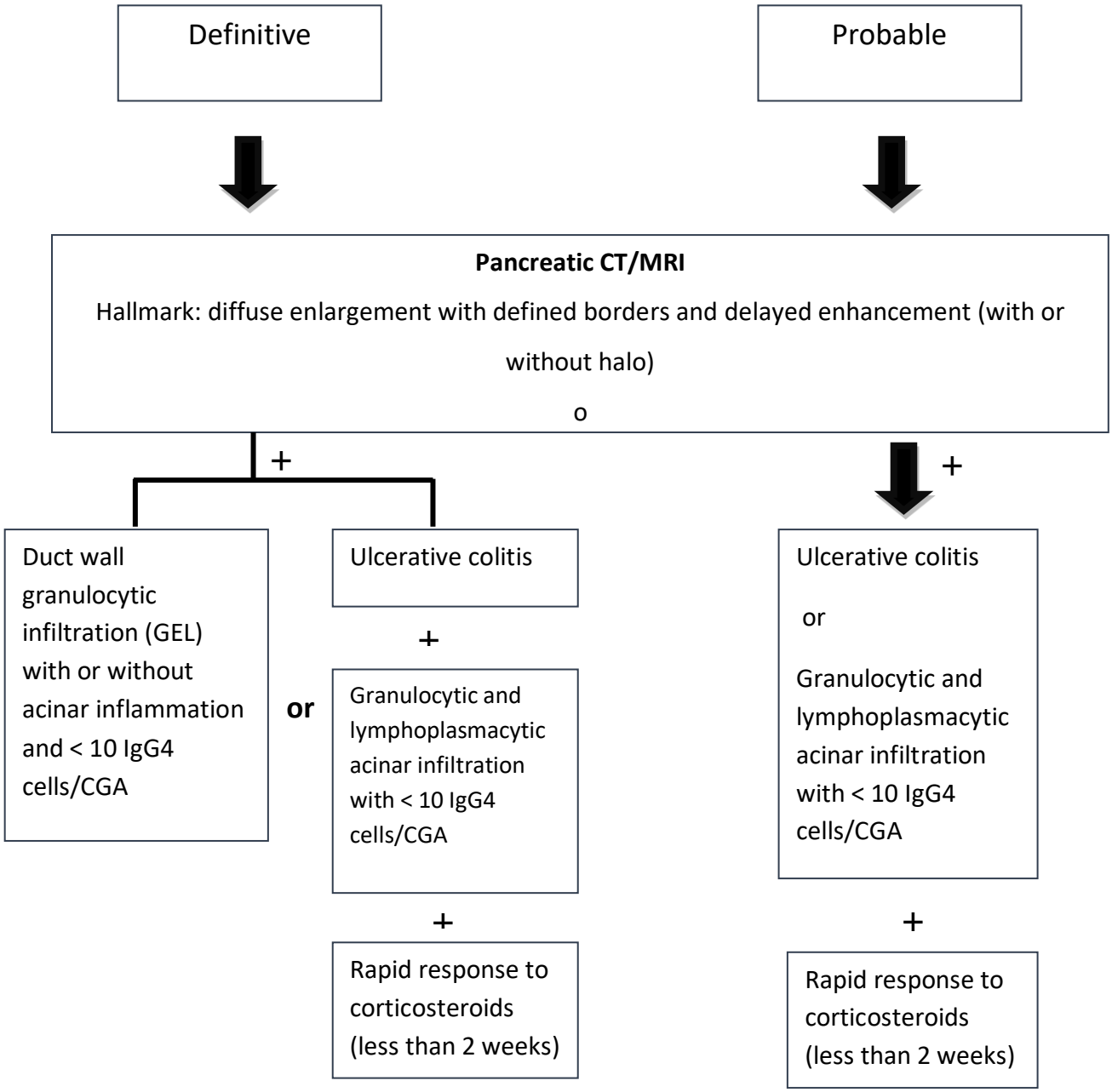

Fig. 1. Diagnostic criteria of autoimmune pancreatitis type 2. According to the 2011 international consensus, the diagnosis is defined as definitive or probable based on imaging test results, histology, association with inflammatory bowel disease and response to corticosteroids. CGA: high-magnification field; GEL: granulocytic epithelial lesion.