

REVIEW ARTICLE

Crohn's Disease and Acute Pancreatitis: A Review of Literature

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ABSTRACT

Crohn's disease, a transmural inflammatory bowel disease, has many well-known extra-intestinal manifestations and complications. Although acute pancreatitis has a higher incidence in patients with Crohn's disease as compared to the general population, acute pancreatitis is still relatively uncommon in patients with Crohn's disease. Patients with Crohn's disease are at an approximately fourfold higher risk than the general population to develop acute pancreatitis. The risk of developing acute pancreatitis is higher in females as compared to males. Acute pancreatitis can occur at any age with higher incidence reported in patients in their 20s and between 40- 50 years of age. The severity and prognosis of acute pancreatitis in patients with Crohn's disease is the same as in general population. Acute pancreatitis can occur before onset of intestinal Crohn's disease, this presentation being more common in children than adults. It can also occur as the presenting symptom. However, most commonly it occurs after intestinal symptoms have manifest with a mean time interval between the initial presentation and development of acute pancreatitis being 2 years. There are several etiological factors contributing to acute pancreatitis in patients with crohn's disease. It is not clear whether acute pancreatitis is a direct extra-intestinal manifestation of Crohn's disease; however majority of the cases of acute pancreatitis in patients with Crohn's disease are due to GS and medications. Drugs used for the treatment of Crohn's disease that have been reported to cause acute pancreatitis include 5-ASA agents, azathioprine and 6 mercaptopurine, metornidazole and corticosteroids. Recent evidence has emerged correlating both type 1 and 2 autoimmune pancreatitis with Crohn's disease. Understanding the association between the two disease entities is key to effectively manage patients with Crohn's disease and acute pancreatitis.

INTRODUCTION

Crohn's disease (CD) is a transmural inflammatory bowel disease (IBD) that can involve any part of the gastro intestinal (GI) tract from mouth to anus. There are many well-known extra-intestinal manifestations and complications of CD [1]. The most common pancreaticobiliary complications of CD are summarized in table 1. Although acute pancreatitis (AP) has a higher incidence in patients with CD as compared to the general population, AP is still relatively uncommon in patients with CD. Multiple factors may contribute to the association of AP with CD. This review article summarizes the current evidence about the etiology, pathogenesis, diagnosis and treatment of AP in patient with CD.

EPIDEMIOLOGY OF AP IN PATIENTS WITH CD

The first association of IBD with AP was made in the 1950s by Ball *et al.* [2] who found in an autopsy series of patient with ulcerative colitis (UC), 53% of the cases had histological evidence of interstitial pancreatitis. In additional 12 % of the cases, histological evidence of definite pancreatic fibrosis and acinar atrophy was noted.

The incidence of AP in patients with CD is much higher than in patients with UC, and the incidence is higher than the general population for both UC and CD. Amongst the several pancreatic complications of CD, AP is the most common. Chronic pancreatitis, exocrine and endocrine pancreatic insufficiency, although reported is much less frequent as compared to AP [3, 4].

The incidence of AP in patients with CD has been reported to be 1.4% in a prospective study carried out in Germany over a period of 10 years [5]. Risk factors for developing AP included younger age (majority of the patients with AP were in their 20s) and female gender (female: male ratio 2:1). Not all the patients had CT abdomen performed, although lipase elevation greater than three times the upper limit of normal was noted in all patients and therefore all the 12 patients met the current American College of Gastroenterology (ACG) criteria for the diagnosis of AP. Surprisingly amylase was not elevated in all cases above three times the upper limit of normal. The reason for this is not clear. It is less likely to be non-specific (non- pancreatic) lipase elevation as the extent of elevation noted was greater than three times the upper limit of normal, and overall lipase is still considered to be more specific than amylase for AP despite an increasing number of entities being reported causing non- specific lipase elevation [6]. The severity and prognosis of AP was noted to be the same as in general population.

A Danish study showed a fourfold increase in risk of AP for patients with CD and a twofold increase in risk of AP for patients with UC as compared to general population during a 16-year period [7]. The highest incidence was noted in the

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Table 1. Pancreaticobiliary complications occurring as a result of Crohn's disease

System involved	Complications
Pancreatic	Acute pancreatitis
	Chronic pancreatitis
	Endocrine and exocrine pancreatic insufficiency
	Gallstones
	Fatty liver
Hepatobiliary	Cirrhosis
	Primary sclerosing cholangitis
	Chronic active hepatitis
	Sclerosing cholangitis
	Splenic vein thrombosis and portal hypertension
Thromboembolic	Portal vein and superior mesenteric vein thrombosis.
	Splenic rupture

age group of 40-49 years in both males and females. The overall risk was higher in women as compared to men. The diagnosis of AP, however, was based on discharge coding. The method used to determine the discharge diagnosis code was not studied. Neither the German or Danish study utilized the current ACG criteria [8] for the diagnosis of AP.

In a more recent study by Moolsintong *et al.* [9], 48 patients with CD and AP were studied over a period of 25 years. The patients were chosen based on a centralized diagnostic index. The incidence was equal between the sexes. The median age was found to be 41 years with a wide range of 14 to 91 years. However, the biochemical criteria used for the diagnosis of AP was lipase and/or amylase elevation greater than two times the upper limit of normal. The current ACG practice guidelines recommend using 3 times the upper limit of normal lipase and/or amylase level for the diagnosis of AP.

RELATIONSHIP OF AP WITH THE INTESTINAL MANIFESTATIONS OF CD

In the vast majority of cases, AP occurs in patients with CD after the diagnosis of CD has been established [5, 7]. Majority of the recent studies looking at AP in patients with CD were carried out in patients with an established diagnosis of CD [5, 7, 10]. Hence, all the patients presented with AP after intestinal manifestations of CD. The majority of the patients presented with AP within 2 years of being diagnosed with CD. The severity of AP was also found to be proportional to the severity of the intestinal manifestations.

In the study by Moolsintong *et al.* [9], the median interval between the time of diagnoses of CD and AP was 7.7 years with a wide range between 20 and 49 years. Only 5 patients (10% of the total) presented with AP before the diagnosis of CD was established. The diagnosis of AP preceded the diagnosis of CD in these patients by a median of 5 days. There have been some case reports of AP presenting before the intestinal manifestations of CD or as a presenting symptom of CD [11, 12, 13]. This presentation is more frequent in children as compared to adults and majority of the reported cases were in the pediatric age group.

DIAGNOSIS OF AP IN PATIENT WITH CD

The current ACG practice guidelines for AP [8] recommend that the diagnosis of AP be made by the presence of 2 out of

the following 3 criteria: 1) Abdominal pain consistent with AP. 2) serum lipase and/or amylase greater than 3 times the upper limit of normal. 3) Characteristic findings from abdominal imaging (contrast enhanced CT or MRI). The diagnosis of AP in patients with CD is challenging as both present with a similar constellation of gastrointestinal signs and symptoms [9, 14].

Nonspecific pancreatic enzyme elevation, without any evidence of AP has been reported previously [15, 16]. Amylase and lipase levels were found to be elevated in 17% and 9% of patients with CD respectively without evidence of true pancreatitis as determined by abdominal ultrasound. High levels of pancreatic enzymes also correlated with extensive CD and a high degree of histological activity. Nonspecific amylase elevation has also been noted in patients with primary sclerosing cholangitis (PSC).

Recurrent abdominal pain is a frequent clinical feature of CD, with abdominal pain being more common in patients with CD as compared to UC. Hence, 2 out of the 3 criteria established by ACG for the diagnosis of AP can be present in patients with CD despite not having true imaging confirmed AP. This could result in a false positive diagnosis of AP. It is not clear how the cut off levels can help with improving the specificity of enzyme elevation for the diagnosis of AP as very high enzyme levels have been reported in patients with CD without AP [17] and the extent of enzyme elevation seen in patients with CD without AP has not been accurately established. In several cases, on the other hand, abdominal pain in patients with CD is often ascribed to active disease and enzyme estimation for AP is never done. As result, the diagnosis of AP could be missed.

In view of these practical difficulties in utilizing the diagnostic criteria proposed by ACG for the diagnosis of AP, in patients with CD, we recommend that any CD patient presenting with abdominal pain consistent with AP be investigated for risk factors for development of AP like gall stones, alcohol abuse or anatomical involvement of the pancreas by CD.

ETIOLOGY OF AP IN PATIENTS WITH CD

Multiple factors may affect prevalence of AP in patients with CD [18]. Gallstones and drugs used for the treatment of CD are the most common etiological factors for AP in patients with CD, anatomical abnormalities and primary sclerosing cholangitis (PSC) being less common [5, 9]. The incidence of alcoholic AP in patients with CD has not been specifically estimated; however it is likely to be the same as the general population. AP may also be an extra-intestinal manifestation of CD with etiological association with CD.

These etiological factors for AP and the reasons for their higher prevalence in patients with CD compared to the general population are discussed in the subsequent sections and summarized in table 2.

GALLSTONES

The prevalence of gall stones in patients with CD is higher than in the general population. The estimated prevalence

Table 2. Etiology of acute pancreatitis in patients with Crohn's disease

Gallstones
Drugs
Anatomical abnormalities
Pancreatic involvement as an extra intestinal manifestation of Crohn's disease

in the general population is approximately 10%, however in patients with CD, the prevalence ranges between 13% to 34% [19-25]. The incidence is higher for all types of gall stones - cholesterol, mixed and pigment-type.

Ileal involvement with the disease or surgical removal of a portion on the ileum interrupts the physiological entero-hepatic circulation of bile acids and reduces their absorption. This leads to a decrease in the amount of hepatic bile which in turn leads to the formation of bile that is supersaturated with cholesterol, ultimately resulting in increased risk for formation of cholesterol gall stones. Also, in patients who have ileal involvement with CD, the mean bilirubin concentration in bile is two to threefold higher than in patients without ileal CD. These patients also have an increased percentage of ursodeoxycholate and a decreased percentage of deoxycholate in bile compared to patients with no ileal CD. This high bilirubin concentration with low percentage of deoxycholic acid in bile favors the formation of mixed and pigment-rich gall stones [26, 27]. Overall, in patients with ileal CD, a threefold higher risk of GS has been noted for both cholesterol and pigment rich gall stones [22].

Also, in patients with ileal and ileocolonic CD, a reduction in gallbladder contractility following fatty meals [28, 29, 30] may contribute to the higher incidence of gall stones in patients with CD, although another study has failed to confirm this hypothesis [31]. This study was performed in 17 patients with CD and 20 healthy age and sex matched controls without gall stones. Ultrasound with volume calculation was used to assess the gallbladder in fasting state and for 10 minutes 70 minutes after ingestion of fat rich meal. Similar methodology was used in the studies that showed a reduction in gallbladder contractility in patient with CD, however these studies had a larger sample size. The mechanism for increased formation of gallstones in patient with CD is summarized in table 3.

Due to the higher prevalence of gallstones in patients with CD, it is prudent to consider measures for prevention of gallstones. Preventive measures known to effective include use of bile acid sequestrant agents like ursodeoxycholic acid and stimulation of cholecystokinin secretion during parental nutrition to induce gallbladder motility. In patient who develops gallstones, the treatment is not different than in general population. If symptomatic gallstones are present, surgical resection of gallbladder is recommended.

DRUGS

There are several medications that have been implicated for causing drug-induced AP in the general population [32, 33]. Because of the practical difficulties in re-challenge, establishing causality is difficult for most of the drugs.

However, amongst the drugs used for the treatment of CD, 5-aminosalicylic acid (ASA) compounds, azathioprine, metronidazole and corticosteroids have been known to cause AP [34]. These agents are summarized in table 4.

Azathioprine (AZA) and 6-Mercaptopurine (6-MP)

AZA is chemically a thioguanine analogue. It is metabolized by the liver into its active metabolite 6-mercaptopurine, which is a T cell inhibitor. AZA is mainly used extensively in maintenance therapy for CD as a steroid sparing agent [35]. The incidence of AZA induced AP in patients with IBD has been reported in older studies to be between 3% to 5% [36]. In a recent long term follow-up study of 3,931 patients carried out in Spain [37] the incidence of AP was reported to be 4%. A higher incidence of AP was seen in patients with CD receiving AZA, as compared to other IBD patients. This is consistent with prior studies that have also reported a higher incidence of AP in patients using AZA for CD as compared to other indications [38, 39]. The reason for this higher incidence is not clear. Interestingly, higher incidence of AP in patients with CD has not been observed with other drugs causing AP. Another recent study carried out in 174 Korean pediatric patients taking AZA, the incidence of AP was reported as high as 7.5% [40]. The mean time between first dose of AZA and development of AP was found to be 19.5 months. Re-challenge was done in 2 patients and recurrence of AP was noted in both. Although there are fewer studies in pediatric age group as compared to adults, the incidence of AP noted in this study was higher than that noted in western pediatric studies [41] where the incidence was noted to be 4.2%.

The mechanism of AZA induced AP is not clear. In cases where re-challenge has been done with AZA, AP developed within 48 hours of re-challenge, suggesting a hypersensitivity reaction as a possible mechanism [42]. Re-challenge is not done routinely, and multiple drugs are often used at the same time, for example AZA and 5-ASA agents, which can cause AP in patients with CD and hence establishment of causality and determination of mechanism for AP are extremely challenging. Auto-antibodies against pancreas (PABs) have been associated with AZA induced AP in CD patients [43]. As discussed in detail in subsequent sections below, it is not clear whether PABs are involved in development of AP in patients with CD.

5- Aminosalicic Acid (ASA) Compounds

Several reports of AP associated with 5-ASA and related medications including sulfasalazine, olsalazine, pentasa and 4-ASA have been published [44-47]. In a large study carried out in United Kingdom [48], the incidence of AP was found to be 7.5/million prescriptions for 5-ASA and

Table 3- Mechanism for increased prevalence of gallstones in patients with Crohn's disease.

Reduced enterohepatic circulation of bile because of Ileal resection
Increased proportion of ursodeoxycholate and reduced proportion of deoxycholate in bile
Reduction in gallbladder contractility

Table 4. Drug induced acute pancreatitis in patients with Crohn's disease

Drug	Incidence	Mechanism	Special Features
Azathioprine (AZA) [1-9]	3-7%	Probably hypersensitivity	-Higher incidence of AP when used for CD -AP associated with PABs reported in patients with CD on AZA
5-ASA agents[10-18]	7.5/million prescriptions for 5-ASA 1.1/million for sulfasalazine	Idiosyncratic, not dose related. Unclear if due to sulfapyridine moiety	-Also reported with rectal 5-ASA administration - Most cases occur within 6 weeks of initiating therapy
Metronidazole[19-26]	Not known, data only from case reports	Unclear. Possibly free radical induced pancreatic damage	- Association probable, not definite
Corticosteroids	Not known	Unclear	- Questionable association

1.1/million prescriptions for sulfasalazine. Most of the cases, in this study and in isolated case reports, have been reported within the first 6 weeks of starting treatment. AP has not been found to be a dose related side effect in most cases. Most of the reported cases of sulfasalazine induced AP that have been reported are mild [44, 47], however one fatal case [46] has also been reported.

Sulfasalazine, the oldest ASA agent used for the treatment of IBD, consists of 5-ASA linked by azo bond to sulfapyridine. The 5-ASA component is largely localized to the colon with minimal systemic absorption, but the sulfapyridine moiety is absorbed systemically. It is believed that the sulfapyridine moiety may be responsible for causing AP, supported by the observation that incidence of AP correlates with sulfapyridine levels and slow acetylator phenotype that leads to prolonged levels of sulfapyridine in blood [49]. However, even with use of 5-ASA medications that lack sulfapyridine moiety, AP still has been reported [50]. 5-ASA rectal enema has also been reported to cause AP [51]. Hence, it is not clear if the sulfapyridine moiety is the etiological factor for 5-ASA compound induced AP. It has also been hypothesized that 5-ASA, acting locally, can increase the pancreatic duct permeability [50] and this might contribute to the development of AP [52].

Metronidazole

Only few case reports have linked metronidazole with development of AP [53-60]. The association is not dose related and the mechanism is not clear. Metronidazole can penetrate pancreatic tissue [61] and is one of the antibiotics recommended for the treatment of infected pancreatic necrosis. It is believed that under aerobic conditions, metronidazole may lead to increased formation of free radicals, thus leading to AP [56].

ANATOMICAL ABNORMALITIES IN CD LEADING TO AP

The mechanism and pathogenesis of AP in duodenal CD are largely based on case reports and individual descriptions [62]. Ampullary obstruction has been proposed as a mechanism of AP in general [63]. In an analysis of 89 cases of duodenal CD by Nugent *et al.* [64], AP was found in 3 cases, and 2 out of the 3 cases were probably related to AZA therapy.

The role of duodenal obstruction in AP is largely theoretical. Obstruction to pancreatic flow from sclerosing papillitis has been reported in case reports [65]. In patients with

duodenal CD, in addition to sclerosing papillitis, development of direct fistula between duodenum and the duct of Wirsung and/or duodenal stricture can occur [66, 67].

IS AP AN EXTRAINTESTINAL MANIFESTATION OF CD?

Extra-intestinal manifestations of IBD involve multiple auto-immune phenomenon [68]. Auto antibodies against exocrine pancreas (PABs) have been reported in patients with CD in particular, and IBD in general. They are measured using indirect immunofluorescent assay. PABs are assumed to be somewhat specific for CD, with prevalence between 41 %-46% in patients with CD reported in a recent study from Greece [69]. The prevalence of PABs in patients with UC was found to be 24.7% in the same study, and the difference between the prevalence of PABs in UC and CD was found to be statistically significant. Despite their relative specificity for CD, the importance of PABs in the pathogenesis of AP in patients with CD is very vague. Several studies [4, 9, 69, 70, 71], have failed to show any correlation between PABs and pancreatic damage in patients with CD. Serum pancreatic enzyme levels do not correlate with PABs [72].

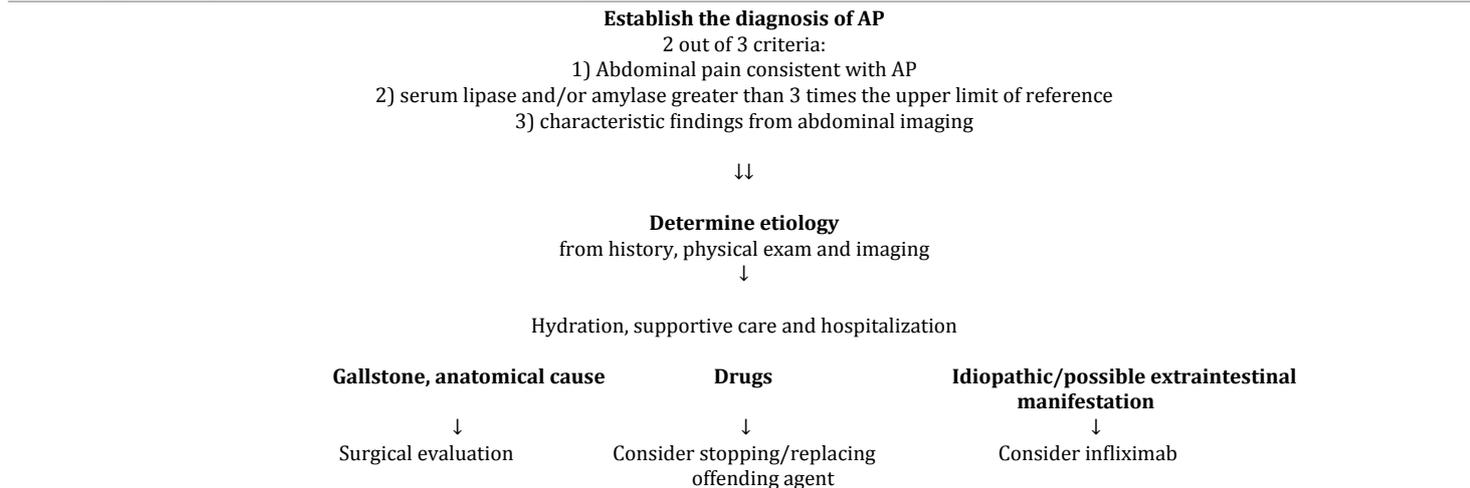
Case reports have been published in literature where granulomatous inflammation in the head of the pancreas has been documented histologically [73]. However, evidence for direct involvement of the pancreas as an extra-intestinal manifestation of CD is limited. It is not clear whether the cases of "idiopathic pancreatitis" reported in patients with CD [10] are truly an extra-intestinal manifestation of CD.

Some recent evidence has emerged supporting the occurrence of AP as a true extra intestinal manifestation of CD. In an animal study carried out on mice [74] migration of mucin 1 (MUC 1)-specific T cells was observed to the colon and the pancreas. MUC 1 is over expressed in a hypoglycosylated form, which is abnormal, on the colonic epithelium in human IBD where it is responsible for inflammation. This migration of MUC 1-specific T cells suggests that pancreatic inflammation is an extra-intestinal manifestation of IBD, characterized by an abnormal expression of pro-inflammatory MUC 1.

Autoimmune Pancreatitis (AIP), Crohn's Disease and IgG4

AIP is a rare autoimmune condition affecting the pancreas. AIP was first reported as a disease entity in 1995 by

Table 5. Approach to patients with Crohn's Disease who develop Acute Pancreatitis



Yoshida *et al.* [75]. AIP mainly affects older men and is characterized by enlargement of the pancreas along with irregular narrowing of the main pancreatic duct and elevation of serum IgG4 [76]. It is classified into two types. Type 1, the most common type worldwide, is associated with extra-pancreatic manifestations and elevated IgG4 levels. Type 2, which is rarer and more difficult to diagnose, is confined to the pancreas. It occurs more often in younger patients and is not associated with elevated IgG4 levels [77].

The association of AIP with UC has been studied and reported [78]. UC is associated with both type 1 and type 2 AIP; however it is more commonly associated with type 2 AIP. UC was diagnosed in 10 out of 64 patients (16%) with type 2 AIP, whereas UC was seen in only 2 out of 153 patients (1%) with type 1 AIP [79]. However, the association of AIP with CD is not as well studied or reported. Only recently evidence has emerged linking CD with AIP. CD has been linked with AIP and IgG4 expression in the ampulla of Vater, distal CBD and ileal pouch-anal anastomosis in the absence of AIP [80, 81, 82]. The presence of IgG4 at these sites was associated with active inflammation, despite immunosuppressive therapy. Serum IgG4 was not elevated and AIP was not present in these patients.

The link between IgG4 expressing plasma cells in the GI tract with IBD in patients who have hepatobiliary manifestations is hypothesized to have diagnostic and therapeutic implications. Further studies exploring this association are awaited.

Currently, not enough evidence exists to support AP as a true extra intestinal manifestation of CD. In patient with CD who develops AP, other etiologies should be ruled out first before ascribing AP to a direct extra intestinal manifestation of CD.

INFLIXIMAB FOR TREATMENT OF PATIENTS WITH "IDIOPATHIC" AP AND CD

It remains to be seen whether the cases of "idiopathic" AP reported in patients with CD are actually an extra-intestinal manifestation of CD. In the absence of clear evidence supporting this, the use of immunosuppressive therapy for

idiopathic AP in patients with CD remains controversial. In a case report, use of Infliximab [83] in patients with idiopathic AP and active CD showed a favorable response. Improvement was noted in both CD and AP with a dose of 5mg/kg body weight at 2 weeks. It remains to be seen if this can be replicated on a large scale in a randomized control trial, however from a practical perspective, Infliximab is perhaps a good choice in patients with active CD who need immunosuppressants as AZA, ASA compounds, corticosteroids and even total parenteral nutrition (TPN) have been associated with AP to some degree.

CONCLUSION

Patients with CD are at an approximately fourfold higher risk than the general population to develop AP. The risk of AP is higher in females as compared to males. AP can occur in CD patients of any age with higher incidence reported in patients in 20s and between 40- 50 years of age. The severity and prognosis of AP in patients with CD is the same as in general population.

AP can occur before onset of intestinal CD, this presentation being more common in children than adults. It can also occur as the presenting symptom. Most commonly, however, it occurs after intestinal symptoms with a mean time interval between initial presentation and development of AP being 2 years.

There are several etiological factors contributing to AP in patients with CD. It is not clear whether AP is a direct extra-intestinal manifestation of CD, however majority of AP in patients with CD are due to GS and medications. Drugs used for the treatment of CD that have been reported to cause AP include 5-ASA agents, AZA and 6 MP, metronidazole and corticosteroids. The evidence for causal association is strongest for AZA and weakest for steroids. In patients with active CD and concomitant AP, perhaps the most reasonable choice of biological agent is Infliximab. It is recommended that patients with CD be on prophylactic treatment to prevent gallstones and get screened for gallstones periodically. Recent evidence has emerged correlating AIP both (type 1 and 2) with CD. The association is, however, not definite. The approach to patients with CD who develop AP is summarized in table 5.

Conflict of Interest

Authors declare to have no conflict of interest.

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