A 60-Year-Old Woman with Primary Biliary Cholangitis and Crohn's Ileitis Following the Suspension of Ursodeoxycholic Acid

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: **Female, 60-year-old**
Final Diagnosis: **Cholangitis • Crohn's disease**
Symptoms: **Asthenia • diarrhea • pruritus**
Medication: **—**
Clinical Procedure: **Endoscopy • MRI**
Specialty: **Gastroenterology and Hepatology**

Objective: **Unusual clinical course**
Background: There is a recognized association between inflammatory bowel disease (IBD) and hepatobiliary autoimmune disease, particularly primary sclerosing cholangitis (PSC). There have been fewer reported cases of IBD and primary biliary cholangitis (PBC), which is treated with ursodeoxycholic acid (UDCA). This report presents the case of a 60-year-old woman with PBC who was diagnosed with Crohn's ileitis after suspension of UDCA treatment.
Case Report: A 66-year-old female patient with PBC was admitted to our department for irrepressible chronic diarrhea and recurrent abdominal pain. PBC was diagnosed on the basis of serological data: chronic (>6 months) increase in alkaline phosphatase (ALP) associated with positivity for specific anti-nuclear antibodies (sp100 and gp210), without requiring a liver biopsy and a magnetic resonance cholangiopancreatography to rule out PSC. Given the intolerance and non-responsiveness according to the Toronto criteria (ALP <1.67 times the normal limit after 2 years) to UDCA at 15 mg/kg/day, an oral monotherapy treatment using obeticholic acid at 5 mg/day was prescribed. The patient complained of abdominal pain and upper gastrointestinal symptoms. The endoscopic/histologic and radiologic examinations supported the diagnosis of Crohn's ileitis. Given the potential benefits to PBC patients of what is described as off-label therapy, budesonide at a dosage of 9 mg/day p.o. was also administered. One month after discharge, an improvement was observed both in the cholestasis indices and in gastrointestinal symptoms.
Conclusions: This report presents a case of PBC in which the patient was diagnosed with Crohn's ileitis after cessation of treatment with UDCA, and highlights the importance of recognizing the association between autoimmune hepatobiliary disease and IBD.

Keywords: **Crohn Disease • Inflammatory Bowel Diseases • Liver Cirrhosis, Biliary**

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936387

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Background

Primary biliary cholangitis (PBC) is a rare chronic inflammatory cholestatic autoimmune liver disease, potentially culminating in end-stage biliary cirrhosis in the absence of adequate treatment [1]. Epidemiologically, this condition represents a female-predominant disease with a typical age of onset of greater than 40 years [2]. The clinical picture of PBC is extremely varied, including common (eg pruritus, abdominal discomfort, sicca complex), possible (eg jaundice, fatigue, restless legs), and rare (eg neurological, including insomnia, depression, and cognitive dysfunction) manifestations [1]. However, an asymptomatic or nonspecific chronic course more often occurs, which delays, unavoidably, the activation of the appropriate diagnostic workup. Currently, PBC diagnosis can be posed in the presence of one of the following serological criteria: (i) an increase in alkaline phosphatase (ALP), maintained for at least 6 months,in the absence of other liver diseases and systemic diseases, associated with either positivity for antimitochondrial autoantibodies (AMA) (titer >1: 40) or antinuclear autoantibodies (ANA) [subtype anti-sp100 and anti-gp210], with the ANA-positive subtype also known as "AMA-negative PBC"; or (ii) a chronic increase in ALP with negative AMA and ANA tests but a liver biopsy that shows destructive cholangitis and destruction of interlobular bile ducts [1,3].

Therefore, liver biopsy is not always required, and appears crucial only when specific antibodies are absent or when coexistence of non-alcoholic steatohepatitis (NASH) or autoimmune hepatitis (AIH) is suspected [3]. The abovementioned serological findings are helpful and sufficient in the differential diagnosis between PBC and primary sclerosing cholangitis (PSC), another cholestatic autoimmune liver disease. However, when the differentiation is doubted, a magnetic resonance cholangiopancreatography (MRCP) could be performed, as MRCP is a test with high specificity and sensitivity for the detection of PSC [3,4]. Different prognostic scores considering clinical, biochemical, and histological findings have been proposed to evaluate the severity of the disease, including the Mayo score, UK-PBC score, and Global PBC Study Group (GLOBE) score [5]. Among these, the Mayo score has been extensively validated and considered the classic prognostic model for survival in untreated PBC patients [5]. Ursodeoxycholic acid (UDCA) at 13-15 mg/kg/day has hugely improved prognosis, and currently represents the first-line treatment [3,4]. The response to UDCA is evaluated on the basis of various criteria, among which the Paris II criteria (ALP level of <1.5 times the normal limit, or an AST level <1.5 times the normal limit, or a bilirubin level <1 mg/dl after one year of treatment) and Toronto criteria (ALP >1.67 times the normal limit after 2 years) represent the most used [6]. In non-UDCA-responsive or UDCA-intolerant patients (people developing adverse drug reactions such as diarrhea), the administration of obeticholic acid (OCA)

has been globally approved in combination with UDCA for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA [1,3]. In these scenarios, OCA represents the exclusive validated second line of treatment, despite encouraging evidence regarding the usefulness of drugs such as bezafibrate and budesonide, which still remain off-label therapies for PBC [7].

Crohn's disease is a chronic inflammatory bowel disease (IBD) clinically associated with progressive bowel damage and disability [8]. The pathogenesis remains unknown and, consequently, despite the availability of several medical agents including mesalazine, locally active steroids (budesonide), systemic steroids, thiopurines (azathioprine), methotrexate, and biological therapies, curative therapy for this condition currently has not been achieved [8]. Crohn's disease diagnosis represents a very complex process: a complete physical examination should be performed, along with laboratory evaluations identifying inflammation markers and screening for alternative diagnoses, including the measurement of fecal calprotectin [9]. Endoscopy and radiological imaging are subsequently used to confirm the diagnosis and determine the extent of the disease [9]. Crohn's disease prognosis can be recurrently severe and unfortunate due to the lack of a definitive cure as well as the various IBD-associated extraintestinal manifestations, which can severely impact the quality of life of patients [8].

In this sense, a recognized association between IBD and hepatobiliary autoimmune disorders, particularly PSC, has been widely described [10,11]. Although the association between IBD and PBC is not as strong as for PSC, anecdotal cases reporting the rare coexistence of IBD and PBC being treated with UDCA do exist [12,13]. In these cases, PBC has usually been identified after IBD was diagnosed [12,13].

This report presents the case of a 60-year-old woman with PBC who was diagnosed with Crohn's ileitis after cessation of treatment with UDCA.

Case Report

A 66-year-old female patient was admitted to our department in November 2021, complaining mostly of fatigue, recurrent abdominal colic, irrepressible chronic diarrhea, and upper gastrointestinal symptoms such as nausea and postprandial distress syndrome dyspepsia.

On admission, the family history showed no clinically relevant information and was negative for both inflammatory and neoplastic gut disorders. Regarding her past medical history, we reported Hashimoto's thyroiditis (diagnosed about 20 years ago, currently in euthyroidism, for which she does not take
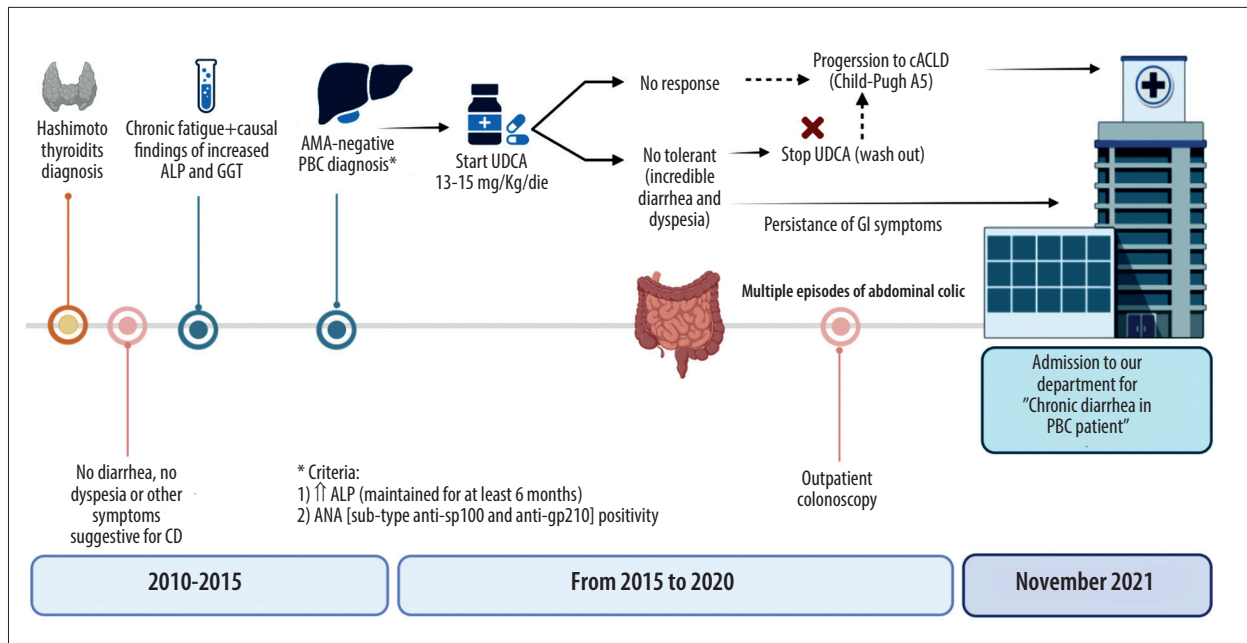
Figure 1. Timeline of clinical events. CD – Crohn's disease; AMA – antimitochondrial autoantibodies; ANA – antinuclear autoantibodies; cACLD – compensated advanced chronic liver disease; GI – gastrointestinal; PBC – primary biliary cholangitis; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; UDCA – ursodeoxycholic acid.

any drug) and PBC (identified after the incidental finding of increased cholestatic indices, more than 5 years ago). She denied other comorbidities as well as previous and current alcohol intake. PBC was diagnosed on the basis of serological criteria: chronic (>6 months) increase of ALP associated with positivity for specific ANA (sp100 and gp210) [3]. In light of this, a liver biopsy and an MRCP to rule out PSC appeared not to be required. UDCA p.o. at 15 mg/kg/day was initially administered using the Toronto criteria (ALP <1.67 times the normal limit after 2 years) to evaluate the response to the treatment over the following 2 years. After 2 years, due both to intolerance (onset of chronic diarrhea) and non-response, the UDCA treatment was ceased. As a consequence, the patient's chronic liver disease progressed to compensated advanced chronic liver disease (cACLD) (Child-Pugh A5). Therefore, after 3 years of UDCA wash-out, an oral monotherapy treatment using OCA at the dosage of 5 mg/day (with a re-evaluation in consideration of a possible increase in dosage to 10 mg after 6 months) was started, according to the current European Association for the Study of the Liver clinical practice guidelines [1].

Starting 1.5 years after the UDCA suspension, the patient complained of recurrent episodes of non-specific colic abdominal pain, but not bloody diarrhea, which forced her to multiple visits to the emergency room. The clinical manifestation was treated with symptom-alleviation drugs without any further medical examination to reach diagnostic conclusions that would have enabled an etiological therapeutic approach. However, she denied vomiting or episodes of sub-occlusive crisis (**Figure 1**).

We also collected documentation of an index endoscopic examination (colonoscopy) performed in June of 2020 highlighting a sub-stenosis of the ileocecal valve. Analysis of the histologic samples obtained from the colonoscopy demonstrated sub-atrophy of the villi and, in the lamina propria, evidence of edema, fibrosis, and vascular congestion. In addition, we observed an active, chronic, lymphoplasmacellular inflammatory infiltrate, organized in lymphofollicular and erosive aspects associated with the coexistence of various eosinophilic granulocytes.

After medical history collection, a physical abdominal examination revealed that the right iliac fossa was slightly painful on palpation. In light of these data, a diagnostic workup protocol for her chronic diarrhea was performed. The results did not provide clear indications (screening for celiac disease: negative, blood eosinophil count: normal; bacterial and parasitic infection panel: negative; endocrine markers of chronic diarrhea: negative), except for the already-known increased cholestasis indices [ALP: ×3 Upper Limit Normal (ULN); gamma-glutamyl-transferase (gamma-GT): ×8 ULN] associated with sp100 and gp120 positivity, an increase in inflammation indices [erythrocyte sedimentation rate: ×2 ULN; C-reactive protein (CRP): ×6 ULN], and a vitamin B12 deficiency. Laboratory investigation results are fully reported in **Table 1**.

Next, endoscopic examinations were performed. Esophagogastroduodenoscopy revealed a picture compatible with "*Helicobacter pylori*-negative hypotrophic pangastropathy (operative link for gastritis assessment=OLGA stage: 0)".

Table 1. Laboratory findings on admission.

Complete blood count		Biochemical features	
RBC (mm³)	4430000	**AST (U/l)**	**44/32**
Hb (g/dl)	13.2	**ALT (U/l)**	**39/33**
WBC (mm³)	3980	**ALP (U/l)**	**282/107**
Neutrophils (mm³)	2000	**Gamma-GT (U/l)**	**287/36**
Eosinophils (mm³)	100	Creatinine (mg/dl)	0.86
PLT (mm³)	217000	Bilirubin (mg/dl)	0.47
Coagulation		Total protein (g/dl)	6.7
PT (%)	104	Albumin (g/dl)	3.9
INR	0.97	Glucose (mg/dl)	88
Fibrinogen (mg/dl)	426	**Total cholesterol (mg/dl)**	**176**
Autoimmunity screening		HDL cholesterol (mg/dl)	59
ANA (sp100 and gp210)	**Positive, titer 1: 80**	CPK (U/l)	18
AMA	Negative	Na⁺ (meq/l)	140
ASMA	Negative	K⁺ (meq/l)	4,1
APCA	Negative	IgG (mg/dl)	982
Anti-TG-IgA	Negative	IgA (mg/dl)	219
Anti-TG-IgG	Negative	IgM (mg/dl)	184
EMA	Negative	**Vitamin B12 (ng/ml)**	**189 (n.v. 200-600)**
Anti-TGB	Negative	Folic acid (ng/ml)	6.7 (n.v. 3-16)
Anti-TPO	Negative	Transferrin (mg/dl)	301
FT4 (pg/ml)	8.2 (n.v. 5.2-15.8)	ESR (mm/h)	44 (n.v. 20)
TSH (microUI/ml)	1.887 (n.v. 0.4-4.0)	**CRP (mg/dl)**	**3 (n.v. 0.5)**
Others			
Fecal calprotectin		Negative	
Bacterial and parasitological examination		Negative	
NSE, chromogranin A		Negative	

RBC – red blood cell count; Hb – hemoglobin; WBC – white blood cell count; PLT – platelets; PT – prothrombin time; INR – International normalized ratio; ANA – antinuclear antibodies; AMA – antimitochondrial antibodies; ASMA – smooth muscle antibodies; TG – transglutaminase; EMA – anti-endomysium autoantibodies; TGB – thyroglobulin; TPO – thyroperoxidase; FT4 – free thyroxin 4; TSH – thyroid-stimulating hormone; AST – aspartate aminotransferase; ALT – alanine amino-transferase; Gamma-GT – gamma-glutamyl transferase; Ig – immunoglobulins; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; n.v. – normal value.

Pancolonscopy confirmed an ileal sub-stenosis: "*Ileocecal valve appears strict, open; the valve is bridled, and, in the ileum, after 2 cm, a sub-stenosis that cannot be passed with a standard instrument is present. No other endoscopic pathologic signs were reported*" (**Figure 2**). Endoscopic mucosal biopsy samples were collected for histologic analysis (**Figure 3**). The conclusion was: "*Chronic inflammatory bowel disease histologic picture, with mild inflammatory activity, compatible with Crohn disease that must be related to the clinical and laboratory findings*".

An MRI enterography was also performed: "*Concentric parietal thickening is found in the last ileal loop, about 21 mm from the sub-stenosing ileocecal valve (maximum wall thickness of 4-8 mm), extending for about 17 mm, and characterized by early transmural enhancement. Further concentric non-stenosing parietal thickening with contrast behavior is found about 20 mm further upstream (maximum wall thickness of 4-6 mm); these findings are associated with mild congestion of the vasa recta ("comb sign") and are compatible with a radiologic picture of*
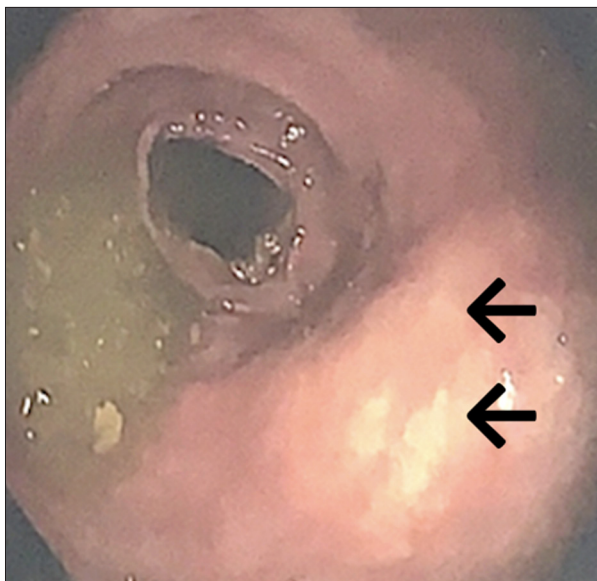
Figure 2. Endoscopic view of the cecum and ileocecal valve (black arrows).

chronic inflammatory disease (Crohn's disease) in the subacute inflammatory phase" [14].

By combining the clinical [Crohn's Disease Activity Index: 215 points], endoscopic [Simple Endoscopic Score for Crohn's Disease: 3], and radiologic (London Score >4.1) pictures, the final diagnosis of active Crohn's ileitis causing ileal sub-stenosis in a patient with concomitant PBC was made [15-17]. Given the concomitance of ileal Crohn's disease and the previously described apparent benefits of off-label therapy for PBC patients [1,3,18], budesonide at a dosage of 9 mg/day p.o. was prescribed.

One month after discharge, at the outpatient check-up, a clear improvement was observed in the cholestasis indices [ALP: <×2 ULN and gamma-GT: ×3 ULN], inflammation indices (CRP: ×2 ULN), and intestinal symptoms (especially in terms of diarrheal and abdominal pain control), revealing an initial success of the combined treatment.

Considering the well-known hepatotoxicity of budesonide in the long term [1,7] as well as the not-excludable possibility of ileal sub-stenosis necessitating a further surgical approach, the patient will need close followup. Therefore, we planned a trimestral followup schedule to manage her biochemical and clinical conditions, adopting a multidisciplinary (hepatologists and IBD experts) management team, which was available in our department.

Discussion

The reported case presents some interesting epidemiological and clinical features offering food for thought on the management of coexisting Crohn's disease and PBC. The patient was a 66-year-old woman for whom the diagnosis of Crohn's disease followed the cessation of treatment with UDCA previously administered for PBC. As she was unable to tolerate the UDCA, to which her PBC was also non-responsive, it was required that completely new and unexplored diagnostic and therapeutic possibilities be considered.

IBD is frequently associated with different extraintestinal manifestations, including various hepatobiliary disorders [19]. It is not clear whether the concomitance of these conditions is accidental or explainable in light of common pathogenetic traits. Corroborating the latter explanation, in the scientific literature, some evidence indicates that these conditions share association with common genetic variants, particularly regarding genes involved in the regulation of immune reactance [20-22]. On the other hand, a large Polish population study has contradicted these data, placing strong doubts on the theory of common genetic background [23]. In our case, the existence of a common denominator linking the diseases based on immune-genetic mechanisms appears reinforced by the concomitant presence in the same patient of an adjunctive autoimmune disease (in addition to her PBC and Crohn's disease): Hashimoto thyroiditis. Thyroid dysfunction is frequently associated with both PBC and Crohn's disease, sometimes preceding the diagnosis of both diseases [24]. Nevertheless, some points concerning the diagnosis and clinical outcome of coexisting PBC and Crohn's disease have to be discussed. Firstly, it is important to consider that, in reporting that "in our patient the onset of PBC occurred before Crohn's disease diagnosis," a point of weakness could exist. On the one hand, she did not present alterations of the alvus or other symptoms suggestive of Crohn's disease before the diagnosis of PBC. On the other hand, IBD might have already been present in a clinically and biochemically silent form. However, the assumption that PBC preceded the onset of Crohn's disease in this patient remains until proven otherwise, since she had never undergone endoscopic examinations with biopsies before being diagnosed with PBC, even if we have to consider the large lapse of time dividing the occurrence of PBC and Crohn's disease.

The second point necessary to be discussed is the correct order of medical events that appear to be relevant to early determination of optimal clinical management. Towards this end, 2 possible scenarios are plausible. In the first scenario, the diagnosis of PBC occurs after a long period of Crohn's disease. In this case, the patient may be a candidate who could benefit from administration of anti-TNF-alpha drugs used for IBD, such as adalimumab or infliximab [8]. In the second scenario, in contrast, the Crohn's disease diagnosis is concomitant or follows that of PBC. In this case, it is likely that the patient has never experienced other drugs for IBD (local or systemic steroids) and/or the disease severity has not reached the
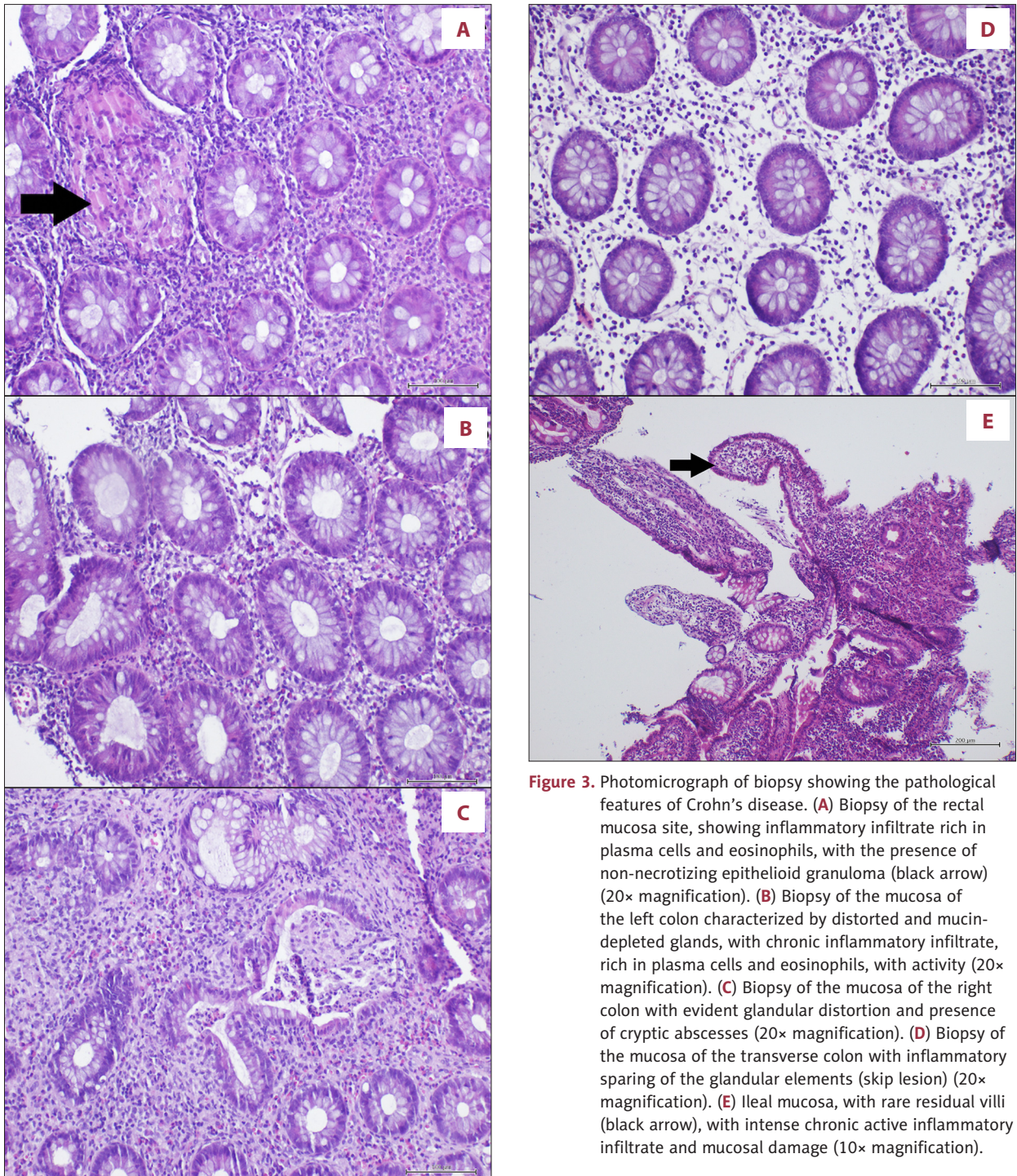
Figure 3. Photomicrograph of biopsy showing the pathological features of Crohn's disease. (**A**) Biopsy of the rectal mucosa site, showing inflammatory infiltrate rich in plasma cells and eosinophils, with the presence of non-necrotizing epithelioid granuloma (black arrow) (20× magnification). (**B**) Biopsy of the mucosa of the left colon characterized by distorted and mucin-depleted glands, with chronic inflammatory infiltrate, rich in plasma cells and eosinophils, with activity (20× magnification). (**C**) Biopsy of the mucosa of the right colon with evident glandular distortion and presence of cryptic abscesses (20× magnification). (**D**) Biopsy of the mucosa of the transverse colon with inflammatory sparing of the glandular elements (skip lesion) (20× magnification). (**E**) Ileal mucosa, with rare residual villi (black arrow), with intense chronic active inflammatory infiltrate and mucosal damage (10× magnification).

point of justification of biological therapies based on anti-TNF-alpha molecules [8].

In the first situation, the drug may be efficacious in treating PBC, as has been described anecdotally in a reported case in which adalimumab resulted in effective control of Hashimoto thyroiditis, Crohn's disease, and PBC in the same patient [25].

Obviously, in this case, PBC-specific treatment based on UDCA (and in the case of failure or intolerance of OCA) must be continued [7]. In the second case, the choice of the most appropriate course of management appears very complex, considering also that there is no evidence justifying the routine clinical use of anti-TNF-alpha as an available drug for PBC patients [7]. The latter appears as the scenario that better reflects the clinical case reported above.

Based on these considerations, therefore, being unable to administer anti-TNF-alpha drugs (both because they are not approved for PBC and because they are not justified by the clinical history of Crohn's disease [8] in the present case report), the best therapeutic strategy appeared to be to treat the PBC with OCA and the Crohn's disease with budesonide. This would also serve to exploit the effects that this steroid can also have on hepatobiliary disease [1,7]. In this regard, a recent placebo-controlled randomized trial on the use of budesonide for PBC following an insufficient response to UDCA demonstrated that budesonide add-on therapy was associated with improvements in biochemical markers of disease activity but no improvement in liver histology [18]. However, careful monitoring needed to be carried out in this patient because budesonide is metabolized for the most part by the liver, and therefore, drug-induced liver injury can sometimes occur [1,7]. In addition, ileal sub-stenosis, if asymptomatic and without a history of sub-occlusive crises, may not benefit from pharmacological treatment alone and may eventually require a surgical approach.

The clinical scenario of co-occurring IBD and hepatobiliary disorders differs from that of PSC, which is often associated with IBD, especially ulcerative colitis. The reported cases of concomitant PBC and Crohn's disease are extremely rare, and existing reports on the coexistence of these 2 conditions typically describe younger patients diagnosed with PBC subsequently to, or concomitantly with, Crohn's disease [12,13,26].

Liberal et al reported a series of 6 patients (including 5 women whose ages ranged from 22.5 to 48.8) with PBC-associated IBD, of which 3 had Crohn's disease and 3 had ulcerative colitis. However, in contrast to our case, in which diagnosis of Crohn's disease occurred after the onset of AMA-negative, UDCA non-responsive PBC, in these abovementioned series, PBC was diagnosed in all of the patients after IBD had been diagnosed. In addition, all of the patients were positive for AMA antibodies, and 1 year after initiation of UDCA, all of the patients responded to therapy [12]. Similarly, other cases of co-occurring Crohn's disease and PBC have been AMA seropositive forms of the hepatobiliary disorder, and, once again, a favorable response to UDCA treatment was seen, as evaluated using Paris II criteria [13].

We report here the case of a 66-year-old female patient, not affected by other comorbidities except for Hashimoto's thyroiditis, in which the onset of AMA-negative PBC preceded ileal Crohn's disease diagnosis. PBC was diagnosed serologically more than 5 years previous to the Crohn's disease diagnosis and was initially treated using UDCA. Unfortunately, after 2 years, the patient had to stop UDCA because of both intolerance (severe diarrhea) and non-responsiveness (according Toronto criteria) [1], facilitating the progression of the disease up to compensated advanced chronic liver disease development.

However, despite the period of UDCA wash-out, diarrheic episodes persisted as well as "upper" gastrointestinal problems (nausea and postprandial distress syndrome dyspepsia), which were associated with worsening fatigue. While the nausea and postprandial distress syndrome dyspepsia could be explained by her autoimmune hepatobiliary disorder, the intractable diarrhea wasn't completely attributable to PBC, especially considering the recurrence of abdominal colic pain episodes. The examinations performed during hospitalization in our department showed the presence of an ileal sub-stenosis with evidence of a histologic sub-acute inflammatory process, compatible with ileal Crohn's disease diagnosis. Therefore, oral administration of budesonide 9 mg/day was started, toward the goal of gaining benefits in treating both PBC and Crohn's disease, through a symbiotic therapeutic effect.

One month after discharge from the hospital, an improvement in cholestasis indices and severity of gastrointestinal symptoms was observed. This confirmed, at least for the moment, the efficacy of the treatment for both diseases. However, considering the hepatotoxicity of budesonide [1,7], as well as the possibility that the ileal sub-stenosis might require surgery, we plan to strictly follow the patient, via a multidisciplinary approach involving hepatologists and IBD experts. Indeed, despite the biochemical and clinical benefits obtained after a month of combined treatment, the case continues to be very complex and the question of whether to consider (and thus treat) the 2 coexisting pathologies as "distinct" or "in parallel" still remains.

In this sense, the best therapeutic strategy dictates that a multidisciplinary approach with close followup over the next few months is crucial.

Conclusions

This report presents a case of PBC in a patient who was diagnosed with Crohn's ileitis after cessation of treatment with UDCA, and highlights the importance of recognizing the association between autoimmune hepatobiliary disease and IBD. Even though this presentation is considered atypical and rare, according to our reported experience, all patients with IBD should be screened not only for PSC but also for other hepatobiliary manifestations, such as PBC, and vice-versa. This could facilitate and optimize the management of both diseases through the early setting of a tailored and adequate therapeutic path.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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