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**Primary sclerosing cholangitis and autoimmune hepatitis overlap syndrome associated with inflammatory bowel disease: A case report and systematic review**

Ballotin VR *et al.* PSC and AIH overlap associated with IBD

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**Abstract**

BACKGROUND

A previously healthy 22-year-old woman presented with abdominal pain and jaundice. She had a reagent antinuclear factor (1:640, with a homogeneous nuclear pattern) and hypergammaglobulinemia (2.16 g/dL). Anti-smooth muscle, anti-mitochondrial and anti-liver-kidney microsomal antibody type 1 antibodies were negative. Magnetic resonance cholangiography showed a cirrhotic liver with multiple focal areas of strictures of the intrahepatic bile ducts, with associated dilations. Liver biopsy demonstrated periportal necroinflammatory activity, plasmocyte infiltration and advanced fibrosis. Colonoscopy showed ulcerative pancolitis and mild activity (Mayo score 1), with a spared rectum. Treatment with corticosteroids, azathioprine, ursodeoxycholic acid and mesalamine was initiated, with improvement in laboratory tests. The patient was referred for a liver transplantation evaluation.

AIM

To report the case of a female patient with autoimmune hepatitis and primary sclerosing cholangitis (PSC) overlap syndrome associated with ulcerative colitis and to systematically review the available cases of autoimmune hepatitis and PSC overlap syndrome.

METHODS

In accordance with preferred reporting items for systematic reviews and meta-analysis protocols guidelines, retrieval of studies was based on medical subject headings and health sciences descriptors, which were combined using Boolean operators. Searches were run on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), Biblioteca Regional de Medicina, Latin American and Caribbean Health Sciences Literature, Cochrane Library for Systematic Reviews and Opengray.eu. Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the studies retrieved were searched manually.

RESULTS

The search strategy retrieved 3349 references. In the final analysis, 44 references were included, with a total of 109 cases reported. The most common clinical finding was jaundice and 43.5% of cases were associated with inflammatory bowel disease. Of these, 27.6% were cases of Crohn’s disease, 68% of ulcerative colitis, and 6.4% of indeterminate colitis. Most patients were treated with steroids. All-cause mortality was3.7%.

CONCLUSION

PSC and autoimmune hepatitis overlap syndrome is generally associated with inflammatory bowel disease and has low mortality and good response to treatment.

**Key words:**Autoimmune hepatitis; Primary sclerosing cholangitis; Crohn’s disease; Ulcerative colitis; Inflammatory bowel diseases

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**Core tip:** We report the case of a female patient with autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) overlap syndrome associated with ulcerative colitis and systematically review the available cases of AIH and PSC overlap syndrome. A previously healthy 22-year-old woman presented with abdominal pain and jaundice. She had a reagent antinuclear factor (1:640, with a homogeneous nuclear pattern). Magnetic resonance cholangiography showed a cirrhotic liver with multiple focal areas of strictures of the intrahepatic bile ducts, with associated dilations. Liver biopsy demonstrated periportal necroinflammatory activity, plasmocyte infiltration, and advanced fibrosis. Colonoscopy showed ulcerative pancolitis and mild activity (Mayo score 1), with a spared rectum. Treatment with corticosteroids, azathioprine, ursodeoxycholic acid and mesalamine was initiated, with improvement in laboratory tests. Searches for systematic reviews were run on seven electronic databases, retrieving 3349 references. In the final analysis, 44 references were included, with a total of 109 cases reported. The most common clinical finding was jaundice and 43.5% of cases were associated with inflammatory bowel disease. Of these, 27.6% were cases of Crohn’s disease, 68% of ulcerative colitis, and 6.4% of indeterminate colitis. Most patients were treated with steroids. All-cause mortality was3.7%. In conclusion, PSC and AIH overlap syndrome is generally associated with inflammatory bowel disease and has low mortality and good response to treatment.

**INTRODUCTION**

Primary sclerosing cholangitis (PSC) is a progressive disorder that causes inflammation and scarring of bile ducts, leading to fibrosis, strictures and dilatation of the biliary tree. These abnormalities are usually identified using cholangiography techniques such as endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography. An exception to this can occur in patients presenting with a rare variant form of PSC called small duct PSC, in which cholangiography findings are absent. The etiology and pathogenesis of PSC are currently unknown, although PSC is highly associated with the presence of inflammatory bowel disease (IBD)[1].

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease with specific laboratory and histological findings. It is characterized by elevated serum aminotransferases, increased total immunoglobulin G (IgG) and positive autoantibodies, whereas liver biopsy may show interface hepatitis and portal mononuclear cell infiltrate[2]. In some cases, patients may present with variant forms of AIH, in which there is an overlap of AIH and another autoimmune liver disease, such as PSC. Therefore, PSC/AIH overlap syndrome (OS) is a rare disorder characterized by the concomitant occurrence of the biochemical and histological features of AIH and the cholangiography abnormalities found in PSC.

In this paper, we report the case of a female patient with PSC/AIH OS associated with ulcerative colitis (UC) and systematically review the literature for available cases of this association.

***Case report***

A previously healthy 22-year-old woman sought medical care due to abdominal pain, jaundice, choluria and acholia that had begun a week before with progressive worsening. There was no report of associated weight loss. She was using oral contraceptives only and denied alcoholism, smoking and drug use.

Laboratory examinations showed hyperbilirubinemia (12.3 mg/dL) with an elevation of direct bilirubin (10 mg/dL), an increase in gamma-glutamyltransferase (165 U/L) and an increase in aspartate aminotransferase and alanine aminotransferase (408 U/L and 277 U/L, respectively). The liver function tests were normal. Serology for hepatitis A, B, C and human immunodeficiency viruses was negative, and IgM serology for cytomegalovirus, Epstein-Barr, and herpes simplex was also negative.

Abdominal ultrasound was performed and the liver showed a diffuse micronodular pattern. Workup was continued through autoimmune markers, urinary copper, serum ceruloplasmin, serum ferritin, transferrin saturation index, and upper abdominal magnetic resonance imaging. The examinations showed a reagent antinuclear factor (1:640, with a homogeneous nuclear pattern) and protein electrophoresis showed hypergammaglobulinemia (2.16 g/dL). Anti-smooth muscle, anti-mitochondrial antibody, and liver-kidney microsomal antibody type 1 were negative.

Magnetic resonance cholangiography showed a reduced-sized liver suggestive of cirrhosis and multiple focal areas of strictures of the intrahepatic bile ducts, with associated dilations (Figure 1). Cholangiography suggested the diagnosis of PSC associated with cirrhosis, and the patient underwent an ultrasound-guided liver biopsy, which showed periportal necroinflammatory activity, plasmocyte infiltration, and advanced fibrosis (Figure 2).

The patient also underwent colonoscopy and endoscopy. Endoscopy did not show esophageal varices and colonoscopy showed changes suggestive of ulcerative pancolitis with mild activity (Mayo score 1), with a spared rectum (Figure 3). Treatment with corticosteroids, azathioprine, ursodeoxycholic acid and mesalamine was initiated, with improvement in laboratory tests, culminating in the normalization of liver transaminases and bilirubin. The patient was referred for a liver transplantation evaluation.

**MATERIALS AND METHODS**

This study was carried out in accordance with the recommendations contained in the preferred reporting items for systematic reviews and meta-analysis protocols guidelines. Our systematic review was registered with the international prospective register of systematic reviews, maintained by York University (registration number CRD42020160708).

***Data sources***

Studies were retrieved using the terms described in the appendix. Searches were run on the electronic databases Scopus, Web of Science, Medline (PubMed), Biblioteca Regional de Medicina, Latin American and Caribbean Health Sciences Literature, Cochrane Library for Systematic Reviews and Opengray.eu. Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the retrieved studies were also searched manually. The databases were searched in December 2019.

***Inclusion criteria and outcomes***

Inclusion criteria were clinical case reports or case series involving AIH and PSC. Exclusion criteria were studies other than case reports or case series and articles that were not related to the topic. If there was more than one study published using the same case, the variables were complemented with both articles. Studies published only as abstracts were included, as long as the data available made data collection possible. The outcome measured was recovery or death.

***Study selection and data extraction***

The search terms used for each database are described in the appendix. An initial screening of titles and abstracts was the first stage to select potentially relevant papers. The second step was the analysis of full-length papers. In this step, some studies were removed due to lack of clinical information. Two independent reviewers (VB, LB) extracted data using a standardized data extraction form after assessing and reaching a consensus on eligible studies. The same reviewers separately assessed each study and extracted data on the characteristics of the subjects and the outcomes measured. A third party (JS) was responsible for divergences in study selection and data extraction, clearing them when required.

***Statistical analysis***

Data are summarized using descriptive analysis–frequency, means and median, using RStudio.

**RESULTS**

***Systematic review***

Using the search strategy, 3349 references were found and 791 references were excluded as they were duplicates. After analyzing the titles and abstracts, 2119 references were excluded and 86 full-text papers were analyzed. In the final analysis, 44 references were included, including 109 cases. A flowchart illustrating the search strategy is shown in Figure 4. The studies included were either a case report or a case series.

Cases from Germany, the United States of America, Czech Republic, Netherlands and Italy were the most common (20.3%, 13.9%, 10.2%, 8.3% and 7.4%, respectively). The baseline features are shown in Table 1. A total of 109 patients were included, 46 (42.59%) were male. Data regarding the sex of 26 patients (24.07%) were not available. All patients were diagnosed with PSC/AIH OS. The age range was 2 to 72 years (mean age was 25 years). Forty-eight (44.44%) patients had IBD. Of these, 13 (27.65%) had Crohn’s disease, 32 (68.08%) had UC and 3 (6.38%) had indeterminate colitis. Only 37 (34.25%) patients did not have IBD, and in 24 (22.22%) the data were NA.

The most common clinical presentation was jaundice, which was present in 31 (28.70%) cases, followed by fatigue and abdominal pain (20.37% and 19.44%, respectively). Hepatomegaly was present in 15 (13.89%) patients and 12 (11.11%) patients had splenomegaly. PSC was identified in small and large ducts (3.70% and 81.48%, respectively). The median score for autoimmune hepatitis was 17 (13-22) pretreatment, and post-treatment was 19 (13-25). Liver biopsy was performed in all patients, and some were classified using the Batts-Ludwig system for grading and staging hepatic inflammation and fibrosis. Cirrhosis was found in 17 (15.74%) patients during follow-up; 2 patients had encephalopathy; 13 (12.03%) patients had esophageal varices; 4 (3.70%) with post-infantile giant cell hepatitis; and only 1 with hepatocarcinoma. Laboratory tests and antibodies are described in Table 1. Human leukocyte antigen and a summary of the clinical cases are described in Table 2[3-46].

The medications administered are described in 63 (58.33%) patients. Of these, 62 (98.41%) patients received steroids; 49 (77.77%) patients received thiopurines (48 on azathioprine and 1 on 6-mercaptopurine) and 7 (11.11%) patients received aminosalicylates (mesalamine); 47 (74.60%) patients received ursodeoxycholic acid. Other medications administered were antibiotics (4.76%), mycophenolate mofetil (3.17%), and D-penicillamine (1.58%). Medication use in 45 (41.66%) of 109 patients was unavailable.

**DISCUSSION**

This is a systematic review of clinical presentations and outcomes of patients with PSC/AIH OS. The findings are described in Tables 1 and 2. In this discussion, unavailable data were not considered[47].

PSC/AIH OS is not an uncommon presentation in the clinic, and occurs in 18% of patients with AIH[48,49]. As previously stated, PSC/AIH OS is characterized by the presence of histologic, serologic, and laboratory features of AIH, with biliary stricture compatible with PSC[50,51]. As described in other studies, it affects predominantly children, adolescents, and young male adults[25,50] which is consistent with our results where the mean age was 25.52 years (22.52-28.51) and the prevalence was higher in men (56,09%). Furthermore, PSC can be divided into large and small ducts, with reports of the latter being rare in the literature[52], which is consistent with our findings, where the prevalence of patients presenting with small-duct PSC was 3.70%.

With regard to the clinical features, most patients present with signs and symptoms of biliary duct involvement[53]. These were common findings in the cases reviewed here and included jaundice, choluria, acholia, and abdominal pain. Moreover, liver function tests in our patient, such as gamma-glutamyltransferase, aspartate aminotransferase and alanine aminotransferase were elevated and were between the confidence interval (95%) described in Table 1 and those in the literature[54]. However, laboratory tests such as total and direct bilirubin were higher levels in the case reported here (12.3 mg/dL and 10 mg/dL, respectively) than in the studies reviewed and described in Table 1. Other tests for viral hepatitis, human immunodeficiency virus, cytomegalovirus, Epstein-Barr, and herpes simplex were negative. Tests for other diseases were performed as part of the diagnostic workup and all were negative. Moreover, the antinuclear antibody was positive in our patient and in the majority of patients described.

Our findings demonstrated an elevated prevalence of IBD with PCS/AIH OS (57.14%), which has been shown in other studies[55,56]. It was reported that UC is found in to up to 16% of patients with AIH[57], whereas, in our study, this association was increased (38.09%), followed by the association with Crohn’s disease (15.47%) and non-specific IBD (3.57%).

Treatment was started and a liver biopsy was performed, which confirmed PSC/AIH OS. The majority of patients in the systematic review were treated with steroids (98.41%) associated with other medications, such as azathioprine or ursodeoxycholic acid. Clinical improvement was satisfactory, leading to recovery in 104 (96.30%) patients. The only patient who received D-penicillamine underwent liver transplantation and later recovered. Our patient started with steroids, azathioprine and mesalamine, with a good clinical response, similar to reports in the literature[58].

The main limitations of our study are the small number of available cases of PSC/AIH OS (*n* = 109) associated with the lack of available data in many of the cases reviewed. As a result, some of the variables described in Table 1 included a small number of patients and, therefore, were statistically insignificant. Moreover, some studies were excluded as individual patient data were NA; thus limiting, even more, the number of cases to be reviewed. Despite these limitations, most of the variables shown in Table 1 were between the confidence interval and this systematic review was able to reinforce some of the literature findings and raise doubts regarding other findings.

In conclusion, PCS/AIH OS has a good response to treatment with steroids, azathioprine and ursodeoxycholic acid and is associated with IBD. It should be suspected in patients with recurrent jaundice, pruritus and abdominal pain or other signals of biliary impairment with suggestive laboratory and imaging tests, especially if associated with IBD. In more severe cases, liver transplantation can be performed[5,6,15,17,20-22,24,25,42] with comparable graft and patient survival, as transplantation-free survival in patients with PSC/AIH OS is worse than that in patients with AIH only[58].

**ARTICLE HIGHLIGHTS**

***Research background***

Primary sclerosing cholangitis (PSC) is a progressive disorder that causes inflammation and scarring of bile ducts, leading to fibrosis, strictures and dilatation of the biliary tree. The etiology and pathogenesis of PSC are currently unknown, although PSC is highly associated with the presence of inflammatory bowel disease (IBD). Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease with specific laboratory and histological findings. It is characterized by elevated serum aminotransferases, increased total IgG and positive autoantibodies, whereas liver biopsy may show interface hepatitis and portal mononuclear cell infiltrate. In some cases, patients may present with variant forms of AIH, in which there is an overlap of AIH and another autoimmune liver disease, such as PSC. Therefore, PSC/AIH overlap syndrome (OS) is a rare disorder characterized by the concomitant occurrence of the biochemical and histological features of AIH and the cholangiography abnormalities found in PSC.

***Research motivation***

Few cases of PSC/AIH OS have been reported in the literature and many questions are unanswered. Thus, the motivation for this systematic review was to clarify questions regarding the epidemiology, clinical presentation, possible treatments and a better understanding of this syndrome.

***Research objectives***

The authors report the case of a female patient with AIH and PSC OS associated with ulcerative colitis and systematically review the available cases of AIH and PSC overlap syndrome.

***Research methods***

This study was carried out in accordance with the recommendations contained in the preferred reporting items for systematic reviews and meta-analysis protocols guidelines. Searches for studies were run on the electronic databases Scopus, Web of Science, Medline (PubMed), Biblioteca Regional de Medicina, Latin American and Caribbean Health Sciences Literature, Cochrane Library for Systematic Reviews and Opengray.eu. Languages were restricted to English, Spanish and Portuguese and there was no date of publication restrictions. The inclusion criteria were clinical case reports or case series involving autoimmune hepatitis and primary sclerosing cholangitis and the exclusion criteria were studies other than case reports or case series and articles that were not related to the topic. Data, such as patients’ clinical presentation and comorbidities, laboratory results, liver biopsy results and medications used were summarized using descriptive analysis – frequency, means and median, using RStudio and the outcome measured was recovery or death.

***Research results***

Forty-four references were analyzed and a total of 109 patients diagnosed with PSC/AIH OS were included. Of these, 46 (42.59%) were male. Forty-eight (44.44%) patients had IBD. The most common clinical presentation was jaundice, which was present in 31 (28.70%) cases, followed by fatigue and abdominal pain (20.37% and 19.44%, respectively). PSC was identified in small and large ducts (3.70% and 81.48%, respectively). Medications were administered in 63 (58.33%) patients. Of these, 62 (98.41%) patients received steroids; 49 (77.77%) patients received thiopurines (48 on azathioprine and 1 on 6-mercaptopurine) and 7 (11.11%) patients received aminosalicylates (mesalamine); 47 (74.60%) patients received ursodeoxycholic acid. Clinical improvement with these treatments was satisfactory, leading to recovery in 104 (96.30%) patients.

***Research conclusions***

AIH/PSC OS has a good response to treatment with steroids, azathioprine and ursodeoxycholic acid and is generally associated with IBD. It should be suspected in patients with recurrent jaundice, pruritus and abdominal pain with laboratory and imaging tests suggestive of both hepatocellular and cholestatic diseases, especially when associated with IBD. In more severe cases, liver transplantation can be performed with comparable graft and patient survival, as transplantation-free survival in patients with PSC/AIH OS is worse than that in patients with AIH only.

***Research perspectives***

From the present study findings, there is no definitive and highly specific clinical presentation of PSC/AIH OS. Therefore, the gastroenterologist should be aware that patients with laboratory data suggestive of both hepatocellular and cholestatic liver injury should undergo liver biopsy in order to achieve an adequate diagnosis, especially if they have a previous diagnosis of IBD. Also, clinical treatment with steroids, azathioprine, and ursodeoxycholic acid seems to be safe and effective and it seems adequate to consider this association in such cases. If medical treatment fails, liver transplantation is also safe and should be considered earlier than with isolated PSC or AIH. The direction of future research should be clinical trials of possible treatments for PSC/AIH OS, as we expect it to become more common, as the prevalence of IBD has been steadily rising in the past decades.

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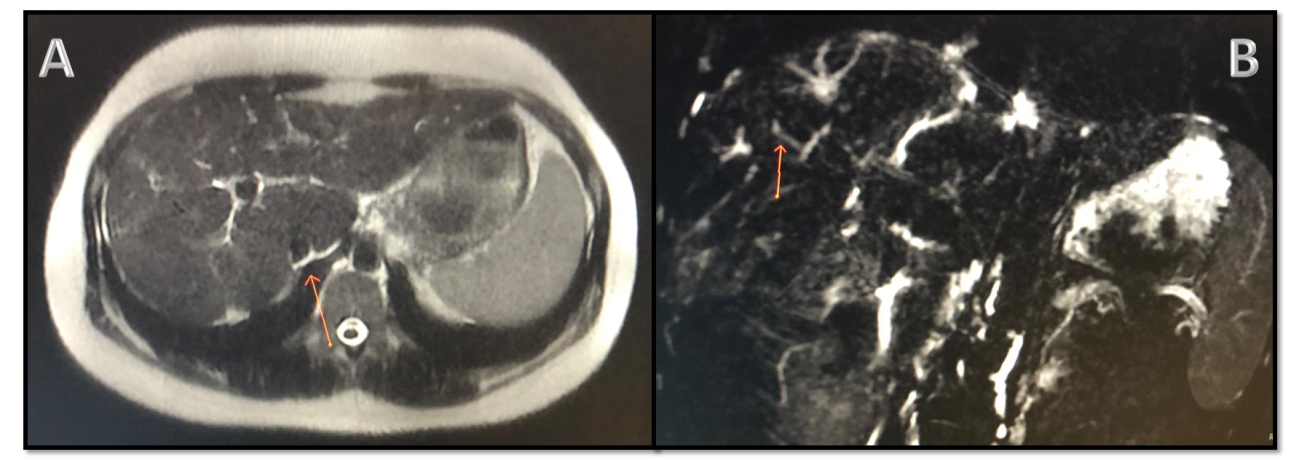
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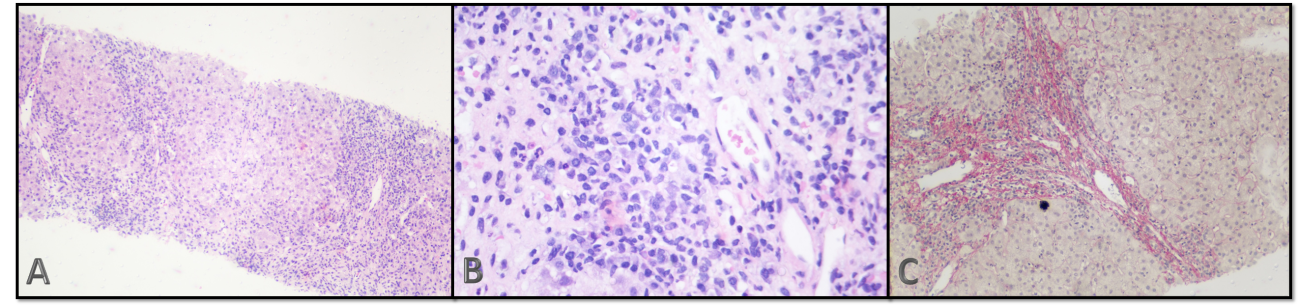
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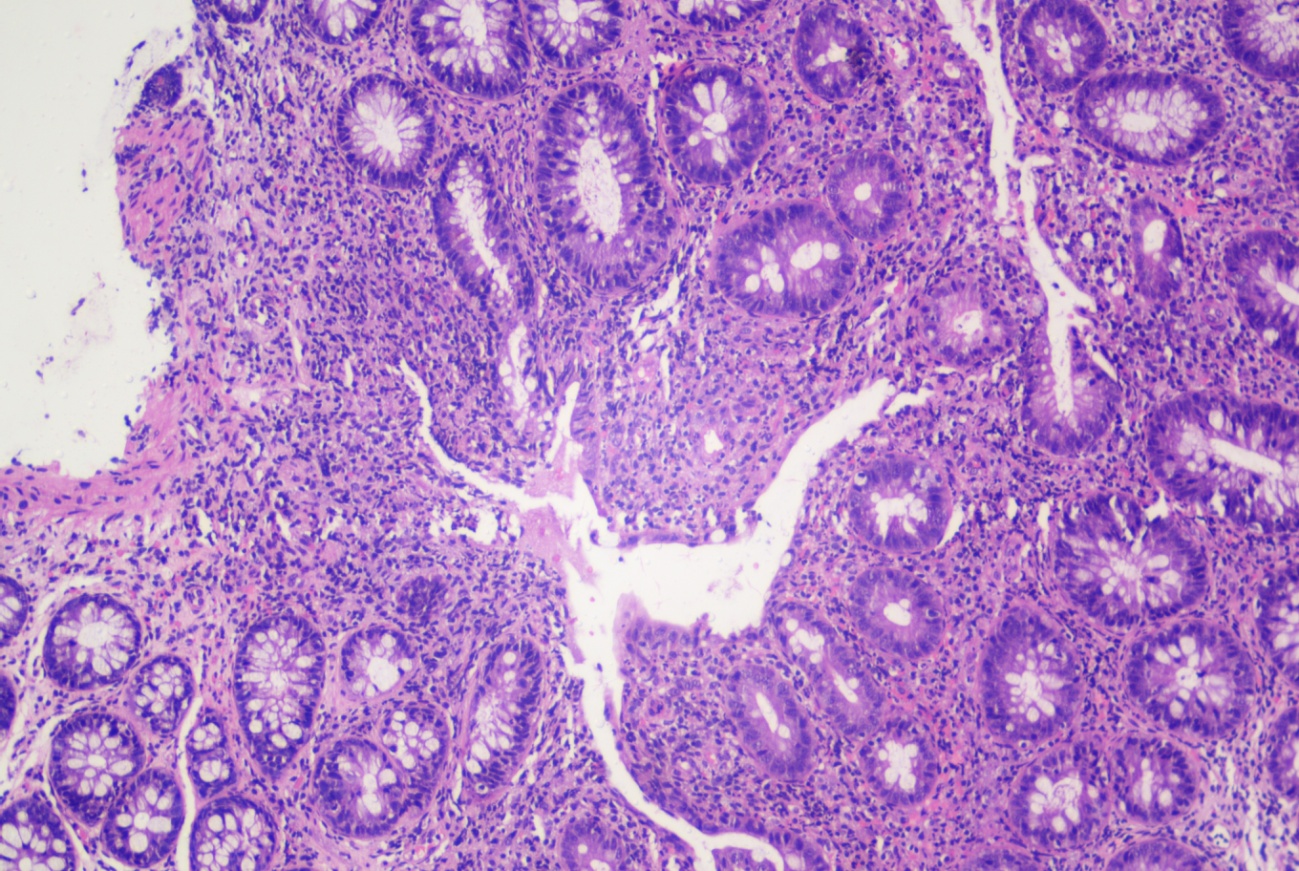
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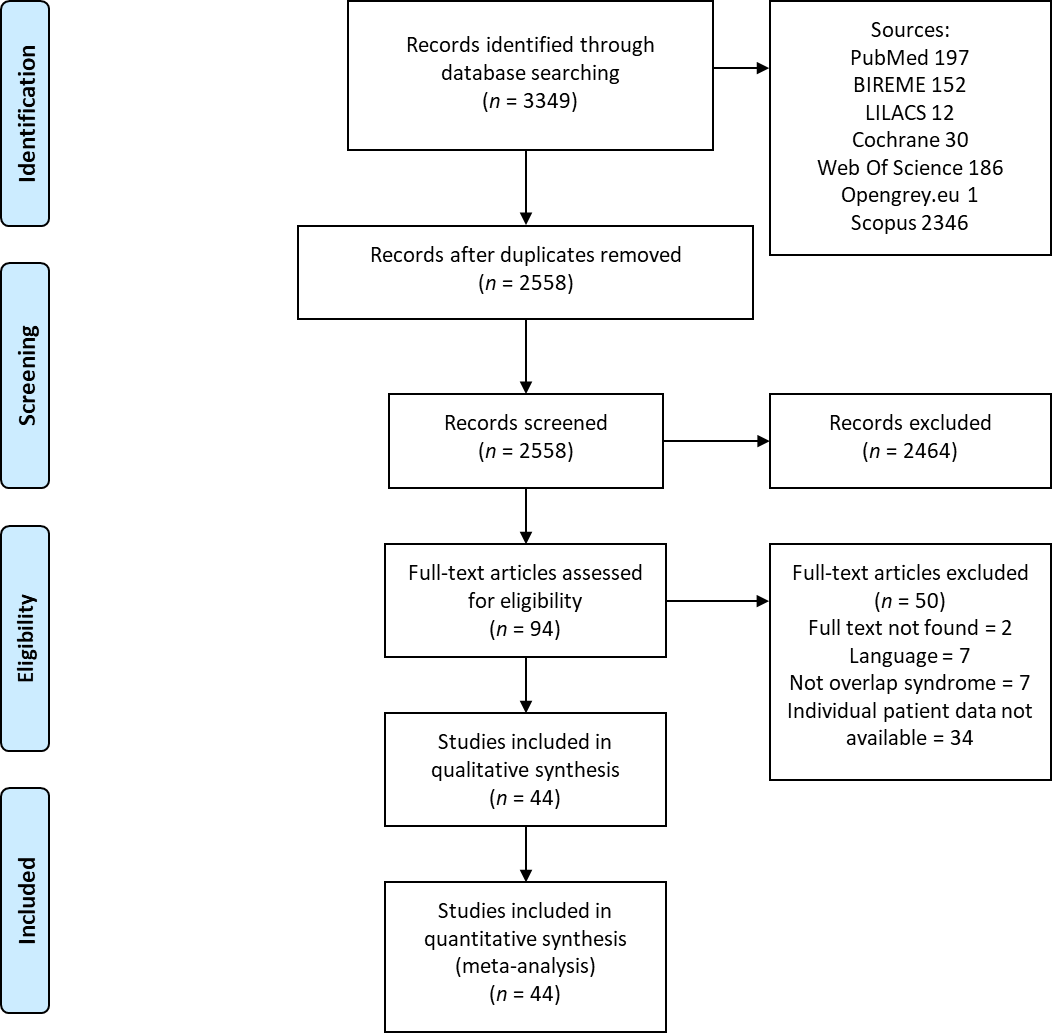
**Figure 1 Magnetic resonance cholangiography.** A: Reduced-sized liver, with lobulated contours and blunt edges, showing caudate lobe hypertrophy and volumetric reduction of the right lobe periphery; B: Multiple focal areas of caliber reduction in the intrahepatic bile duct, with upstream biliary ectasia, associated with signs of distortion of the usual architecture and parietal irregularities in the bile duct.



**Figure 2 Liver biopsy.** A: Intense increase in periportal necroinflammatory activity (Hematoxylin-eosin staining 40 ×); B: Grouping of periportal plasmocyte cells (Hematoxylin-eosin staining 100 ×); and C: Fibrosis in red demarking a nodule (Picro Sirius Red 100 ×).



**Figure 3 Ascending colon, biopsy.** Area of erosion in the ascending colon (Hematoxylin-eosin staining 100 ×).



**Figure 4 Prisma flowchart.**

**Table 1 Baseline features in 109 patients with overlap syndrome (primary sclerosing cholangitis/autoimmune hepatitis)**

|  |  |
| --- | --- |
| **Variable** | **Patients (*n* = 109)** |
| Mean age (yr) | 25.52 |
| Sex (male) | 46 (42.59%) |
| Race | 10 (6.78%) |
| White | 7 (70%) |
| Black | 3 (30%) |
| IBD | 48 (44.44%) |
| CD | 13 (27.65%) |
| UC | 32 (68.08%) |
| Non-specific | 3 (6.38%) |
| PSC |  |
| Small Ducts | 4 (3.70%) |
| AIH (median) |  |
| SAH pre-treatment (pts) | 17 (13-22) |
| SAH post-treatment (pts) | 19 (13-25) |
| Clinical Presentation |  |
| Fever | 7 (6.48%) |
| Dyspnea | 1 (0.93%) |
| Headache | 1 (0.93%) |
| Jaundice | 31 (28.70%) |
| Pruritus | 11 (10.19%) |
| Urine Alteration | 6 (5.55%) |
| Choluria | 5 (83.33%) |
| Hematuria | 1 (16.66%) |
| Nausea | 4 (3.70%) |
| Emesis | 8 (7.40%) |
| Without Blood | 4 (50%) |
| Hematemesis | 4 (50%) |
| Diarrhea | 11 (10.19%) |
| Stools | 18 (16.66%) |
| Hematochezia | 1 (5.55%) |
| Melena | 1 (5.55%) |
| Incontinence | 1 (5.55%) |
| Acholia | 3 (16.66%) |
| Watery Stools | 11 (61.11%) |
| Steatorrhea | 1 (5.55%) |
| Abdominal Pain | 21 (19.44%) |
| Joint Pain | 2 (1.85%) |
| Weight Loss | 9 (8.33%) |
| Fatigue | 22 (20.37%) |
| Family History | 4 (3.70%) |
| Hepatomegaly | 15 (13.89%) |
| Splenomegaly | 12 (11.11%) |
| Ascites | 7 (6.48%) |
| Fecal Occult Blood | 3 (2.78%) |
| Cirrhosis | 17 (15.74%) |
| Encephalopathy | 2 (1.85%) |
| Comorbidities |  |
| Esophageal Varices | 13 (12.03%) |
| Hypothyroidism | 1 (0.93%) |
| Anemia | 1 (0.93%) |
| Alcohol-induced pancreatitis | 1 (0.93%) |
| Hepatic insufficiency | 1 (0.93%) |
| Rheumatoid Arthritis | 1 (0.93%) |
| Smoker | 1 (0.93%) |
| Membranous Glomerulonephritis | 1 (0.93%) |
| Hepatocarcinoma | 1 (0.93%) |
| Pyoderma Gangrenosum | 1 (0.93%) |
| Reflux Nephropathy | 1 (0.93%) |
| Post-infantile Giant Cell Hepatitis | 4 (3.70%) |
| Renal Cell Carcinoma | 1 (0.93%) |
| Autoimmune Thyroiditis | 1 (0.93%) |
| Biopsy | 109 (100%) |
| Grade (Batts-Ludwig) | 29 (26.85%) |
| None | 2 (6.89%) |
| Minimal | 1 (3.44%) |
| Mild | 10 (34.48%) |
| Moderate | 11 (37.93%) |
| Severe | 5 (17.24%) |
| Stage (Batts-Ludwig) | 37 (34.25%) |
| None | 1 (2.70%) |
| Portal Fibrosis | 14 (37.83%) |
| Periportal Fibrosis | 10 (27.02%) |
| Septal Fibrosis | 9 (24.32%) |
| Cirrhosis | 3 (8.10%) |
| Laboratory tests (mean) |  |
| Hb (g/dL) | 10.20 |
| Ht (%) | 32.8 |
| Leucocytes (mm3) (median) | 7600 |
| Platelets (mm3) (median) | 185000 |
| Prothrombin time (s) | 15.35 |
| INR | 1.41 |
| ALT (U/L) | 378.2 |
| AST (U/L) | 378.2 |
| GGT (U/L) | 316.6 |
| ALP (U/L) | 693.4 |
| Total Bilirubin (mg/dL) | 5.14 |
| Direct Bilirubin (mg/dL) | 4.43 |
| Total Protein (g/dL) | 17.82 |
| Albumin (g/dL) (median) | 3.09 |
| Total globulins (mg/L) | 51410 |
| IgG total (mg/dL) | 2762 |
| IgA total (mg/dL) | 230.3 |
| IgM total (mg/dL) | 729.7 |
| Antibodies |  |
| LKM1 | 3 (2.78%) |
| AMA | 3 (2.78%) |
| ANA | 59 (54.63%) |
| SMA | 33 (30.56%) |
| pANCA | 36 (33.33%) |
| HLA | 18 (16.66%) |
| Medications | 63 (58.33%) |
| Steroids | 62 (98.41%) |
| Azathioprine | 48 (76.19%) |
| 6-mercaptopurine | 1 (1.58%) |
| Ursodeoxycholic acid | 47 (74.60%) |
| Mesalazine | 7 (11.11%) |
| Antibiotics | 3 (4.76%) |
| D-penicillamine | 1 (1.58%) |
| Cyclosporine A | 1 (1.58%) |
| Mycophenolate mofetil | 2 (3.17%) |
| Clinical Improvement | 61 (56.48%) |
| Relapse | 41 (37.96%) |
| Transplantation | 13 (12.87%) |
| Mean time from diagnosis-transplant (mo) *n* = 10 (76.92%) | 74.90 |
| Transplant medications *n* = 4 | 4 (30.76%) |
| Steroids | 4 (100%) |
| Basiliximab | 1 (25%) |
| Cyclosporine | 2 (50%) |
| Azathioprine | 1 (25%) |
| Tacrolimus | 2 (50%) |
| Mycophenolate mofetil | 2 (50%) |
| Mean time follow-up (mo) | 59.18 |
| Death | 4 (3.70%) |

IBD: Inflammatory bowel disease; CD: Crohn’s disease; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis; AIH: Autoimmune hepatitis; SAH: Score for autoimmune hepatitis; INR: International normalized ratio; ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; LKM1: Liver kidney microsome type 1 antibody; AMA: Anti-mitochondrial antibodies; ANA: Antinuclear antibody; SMA: Smooth muscle antibodies; pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies.

**Table 2 Summary of systematically reviewed clinical cases (primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Sex** | **Age** | **Clinical presentation** | **IBD** | **Co-morbidities** | **Antibodies** | **HLA** | **Treatment** | **Relapse** | **Outcome** | **Miscellaneous** |
| W*urbs et al*[3], 1995 | Germany | F | 28 | Fever, Choluria, Weight Loss, Fatigue | N | None | pANCA, SMA | DR | Steroids, AZA | N | Recovery |  |
| Lawrence *et al*[4], 1994 | United States | M | 39 | Nausea, Emesis, Fatigue, Hepatomegaly, Occult stool blood | UC | Cirrhosis | SMA | NA | Steroids, AZA, Cyclosporine A | N | Recovery |  |
| Nalepa *et al*[5], 2017 | Poland | M | 10 | Jaundice, Diarrhea, Abdominal Pain, Hepatomegaly, Splenomegaly, Ascites, Hematemesis | UC | Cirrhosis, Esophageal Varices | ANA, SMA | NA | Steroids, AZA, UDCA, MSM | Y | Recovery | Liver transplantation |
| Luketic *et al*[6], 1997 | United States | F | 38 | Jaundice, Nausea, Fatigue, Ascites, Hematemesis | N | None | ANA | NA | Steroids, AZA | Y | Recovery | Liver transplantation |
| Mueller *et al*[7], 2018 | Germany | F | 15 | Vomiting, Fatigue | N | None | ANA, pANCA, SMA, AMA | NA | Steroids, UDCA | N | Recovery |  |
| Guerrero-Hernández *et al*[8], 2007 | Mexico | F | 22 | Jaundice, Choluria, Fatigue | N | None | ANA, pANCA | NA | Steroids, AZA, UDCA | N | Recovery |  |
| Takiguchi *et al*[9], 2002 | Japan | F | 36 | Fever | N | None | ANA, pANCA | A24, A31, B35, B61, Cw4,  DR4 | Steroids, AZA, UDCA | Y | Recovery |  |
| McNair *et al*[10], 1998 | United Kingdom | M | 38 | Jaundice, Watery Stools, Abdominal Pain, Weight Loss | UC | Encephalopathy | ANA, LKM1, pANCA, SMA | B8, DR3 | Steroids, AZA | Y | Death |  |
| McNair *et al*[10], 1998 | United Kingdom | F | 20 | Jaundice, Itching | N | None | ANA, pANCA, SMA | ND | Steroids, AZA, UDCA | Y | Recovery |  |
| McNair *et al*[10], 1998 | United Kingdom | M | 26 | Dyspnea, Jaundice | N | None | ANA, pANCA | A1, B8, DR3 | Steroids, AZA | Y | Recovery |  |
| McNair *et al*[10], 1998 | United Kingdom | M | 14 | Jaundice, Diarrhea, Abdominal Pain | UC | None | ANA, pANCA, SMA | A1, B8, DR3 | Steroids, AZA | Y | Recovery |  |
| McNair *et al*[10], 1998 | United Kingdom | M | 18 | Jaundice, Diarrhea, Abdominal Pain, Weight Loss | N | None | pANCA, SMA | ND | Steroids, AZA, UDCA | N | Recovery |  |
| Man *et al*[11], 2017 | Romania | M | 13 | Jaundice, Hepatomegaly, Splenomegaly | N | Esophageal Varices | SMA | NA | Steroids, AZA, UDCA, Mycophenolate Mofetil | Y | Recovery |  |
| Malik *et al*[12], 2010 | United States | F | 22 | Diarrhea, Abdominal Pain | CD | None | NA | NA | Steroids, AZA, UDCA, Mycophenolate Mofetil | Y | Recovery |  |
| Lamia *et al*[13], 2012 | Tunisia | M | 4 | Hematuria, Diarrhea, Hepatomegaly, Splenomegaly | NSIC | None | ANA, pANCA, SMA | NA | Steroids, AZA, UDCA, 6-MP | Y | Recovery |  |
| Lee *et al*[14], 2005 | Malaysia | F | 5 | Jaundice, Itching, Steatorrhea | N | None | ANA, SMA | NA | Steroids, UDCA | N | Recovery |  |
| Santos *et al*[15], 2012 | Colombia | M | 36 | Jaundice, Hematemesis, Abdominal Pain, Hepatomegaly, Ascites | N | Cirrhosis, Encephalopathy, Esophageal Varices | ANA | NA | Steroids, AZA, UDCA | Y | Recovery | Liver transplantation |
| Santos *et al*[15], 2012 | Colombia | F | 35 | Headache, Jaundice, Fatigue | UC | Esophageal Varices | ANA, pANCA, SMA | NA | Steroids, UDCA, MSM | Y | Recovery |  |
| Santos *et al*[15], 2012 | Colombia | F | 45 | Jaundice, Choluria, Acholia, Hepatomegaly | NSIC | Hypothyroidism | ANA, SMA | NA | Steroids, AZA, UDCA | N | Recovery |  |
| Saltik-Temizel *et al*[16], 2004 | Turkey | M | 11 | Jaundice, Itching, Abdominal Pain, Hepatomegaly, Splenomegaly, Fecal Occult Blood | UC | None | pANCA, SMA | NA | Steroids, AZA, UDCA, MSM | Y | Recovery |  |
| Gopal *et al*[17], 1999; Nagral *et al*[18], 1999 | India | F | 14 | Jaundice, Hepatomegaly, Splenomegaly, Ascites | N | Cirrhosis, Esophageal Varices | ANA | NA | Steroids, D-penicillamine | Y | Recovery | Liver transplantation |
| Lüth *et al*[19], 2009 | Germany | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Farid *et al*[20], 2015 | Bahrain | F | 11 | Jaundice, Nausea, Vomit, Abdominal Pain | UC | Cirrhosis | NA | NA | Steroids, AZA | Y | Death | Liver transplantation |
| Floreani *et al*[21], 2005 | Italy | F | 26 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Floreani *et al*[21], 2005 | Italy | M | 19 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Floreani *et al*[21], 2005 | Italy | M | 32 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Floreani *et al*[21], 2005 | Italy | M | 27 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Floreani *et al*[21], 2005 | Italy | F | 15 | NA | NA | NA | NA | NA | NA | NA | NA | Liver transplantation |
| Floreani *et al*[21], 2005 | Italy | F | 15 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Floreani *et al*[21], 2005 | Italy | F | 16 | NA | NA | NA | NA | NA | NA | NA | NA |  |
| Gohlke *et al*[22], 1996; Zenouzi *et al*[23], 2014 | Germany | M | 19 | NA | N | Esophageal Varices | ANA, pANCA, SMA | A1, A32, B8, Cw3, Cw7, DR3, DR4 | Steroids, AZA, UDCA | Y | Recovery |  |
| Gohlke *et al*[22], 1996; Zenouzi *et al*[23], 2014 | Germany | M | 28 | NA | UC | Esophageal Varices | ANA, pANCA | A1, A32, B7, B8, Cw7, DR3, DR4, DR52, DR53, DQ2, DQ3 | Steroids, AZA, UDCA | Y | Recovery |  |
| Gohlke *et al*[22], 1996; Zenouzi *et al*[23], 2014 | Germany | M | 18 | NA | N | Cirrhosis, Esophageal Varices | ANA, pANCA, SMA | A1, A25, B8, DR3 | Steroids, AZA, UDCA | Y | Recovery | Liver transplantation |
| Abdo *et al*[24], 2002 | Canada | M | 15 | Jaundice, Fatigue | UC | None | ANA, SMA | NA | Steroids, AZA | Y | Recovery |  |
| Abdo *et al*[24], 2002 | Canada | M | 51 | Abdominal Pain, Weight Loss, Fatigue | N | None | ANA, SMA | NA | Steroids, AZA, UDCA | Y | Recovery |  |
| Abdo *et al*[24], 2002 | Canada | M | 54 | Abdominal Pain, Fatigue, Splenomegaly | UC | Cirrhosis, Alcohol-induced Pancreatitis | NA | NA | Steroids, AZA, UDCA, MSM | Y | Recovery |  |
| Abdo *et al*[24], 2002 | Canada | F | 25 | Jaundice, Itching, Abdominal Pain, Fatigue, Hepatomegaly | N | None | ANA, SMA | NA | Steroids, AZA, UDCA | Y | Recovery |  |
| Abdo *et al*[24], 2002 | Canada | F | 23 | Fatigue | UC | None | ANA, SMA | NA | Steroids, AZA, UDCA, MSM | Y | Recovery |  |
| Abdo *et al*[24], 2002 | Canada | M | 20 | Jaundice, Abdominal Pain, Weight Loss, Hepatomegaly, Splenomegaly | N | Cirrhosis | ANA, SMA | NA | Steroids, AZA, UDCA | Y | Recovery | Liver transplantation |
| van Buuren *et al*[25], 2000 | Netherlands | M | 7 | NA | UC | None | ANA, SMA | NA | Steroids, AZA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | M | 14 | NA | CD | None | ANA, SMA | NA | Steroids, AZA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | F | 21 | NA | UC | None | ANA, pANCA | NA | Steroids, AZA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | F | 22 | NA | CD | None | ANA, SMA | NA | Steroids, AZA | Y | Recovery | Liver transplantation |
| van Buuren *et al*[25], 2000 | Netherlands | M | 20 | NA | UC | None | SMA | NA | Steroids, AZA, UDCA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | M | 23 | NA | UC | Cirrhosis, Esophageal Varices | ANA, pANCA | NA | Steroids, AZA, UDCA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | M | 37 | NA | N | None | ANA | NA | Steroids, AZA, UDCA | NA | Recovery |  |
| van Buuren *et al*[25], 2000 | Netherlands | M | 54 | NA | CD | None | ANA, SMA | NA | Steroids, AZA, UDCA | Y | Recovery | Liver transplantation |
| van Buuren *et al*[25], 2000 | Netherlands | F | 44 | Jaundice | UC | Hepatic Insufficiency | pANCA | NA | Steroids, AZA, UDCA | Y | Recovery | Liver transplantation |
| Li *et al*[26], 2017 | China | M | 52 | Jaundice, Itching | N | Rheumatoid Arthritis | NA | NA | Steroids | N | Recovery |  |
| Gharibpoor *et al*[27], 2017 | Iran | M | 26 | Jaundice, Itching, Choluria, Acholia, Abdominal Pain, Weight Loss, Hepatomegaly | N | None | ANA, SMA | NA | Steroids, AZA, UDCA | N | Recovery |  |
| Sander *et al*[28], 2007 | Germany | M | 24 |  | CD | None | ANA, SMA | B8, DR4 | Steroids, AZA, UDCA | Y | Recovery |  |
| Smolka *et al*[29], 2016 | Czech Republic | M | 16 | Jaundice | N | None | ANA, pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | M | 17 | Diarrhea, Abdominal Pain | UC | None | pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 15 | Fatigue | N | None | pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | M | 14 |  | UC | None | NA, pANCA, SMA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 16 |  | CD | None | pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 10 | Fever, Weight Loss, Fatigue | NSIC | None | LKM1, pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | M | 12 | Abdominal Pain | UC | None | pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 9 | Melena, Fatigue | UC | None | ANA, pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | M | 3 | Diarrhea, Abdominal Pain | UC | None | ANA, pANCA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 9 |  | N | None | ANA, pANCA, SMA | NA | NA | NA | NA |  |
| Smolka *et al*[29], 2016 | Czech Republic | F | 15 | Itching, Diarrhea, Abdominal Pain | CD | None | ANA, pANCA | NA | NA | NA | NA |  |
| Griga *et al*[30], 2000 | United Kingdom | F | 24 | Diarrhea | CD | None | ANA, pANCA | NA | Steroids, MSM, UDCA | N | Recovery |  |
| Griga *et al*[30], 2000 | United Kingdom | M | 28 | Jaundice, Itching | N | None | ANA, pANCA | B8, DR4 | Steroids, UDCA | N | Recovery |  |
| Warling *et al*[31], 2014 | Belgium | M | 29 | Jaundice, Fatigue | UC | Membranous Glomerulonephritis | pANCA | DR3 | Steroids, AZA, UDCA, MSM, 6-MP | Y | Recovery |  |
| Hyslop *et al*[32], 2010 | United States | NA | 40 | NA | UC | None | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 24 | NA | UC | None | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 53 | NA | CD | Cirrhosis | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 37 | NA | UC | None | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 32 | NA | UC | Cirrhosis | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 61 | NA | CD | Cirrhosis | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 52 | NA | CD | None | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 26 | NA | CD | Cirrhosis | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 33 | NA | UC | None | ANA | NA | NA | NA | NA |  |
| Hyslop *et al*[32], 2010 | United States | NA | 44 | NA | UC | Cirrhosis | ANA | NA | NA | NA | NA |  |
| Fukuda *et al*[33], 2012 | Japan | M | 72 | Ascites | N | Cirrhosis, Hepatocellular Carcinoma | ANA, AMA | DRB1\*0405, DRB1\*0901 | Steroids, UDCA | Y | Death |  |
| Hatzis *et* *al*[34], 2001 | Greece | F | 46 | Fever, Arthralgia, Fatigue, Splenomegaly | N | Nephrectomy for Reflux Nephropathy | ANA, pANCA, SMA | A3, A11, B16, B35, Cw4, DR13, DR14, DR52, DQ6 | Steroids, AZA, UDCA, Antibiotics | N | Recovery |  |
| Thakker *et al*[35], 2010 | India | F | 9 | Fever, Jaundice, Itching, Arthralgia, Fatigue, Hepatomegaly, Splenomegaly | N | None | ANA | NA | Steroids, UDCA | N | Recovery |  |
| Koskinas *et al*[36], 1999 | Greece | M | 18 | Fever, Jaundice, Hematochezia, Fatigue, Hepatomegaly, Splenomegaly, Ascites | UC | Pyoderma Gangrenosum | NA | A2, A32, B7, B21, B49, Bw4, Bw6, DR6, DR10, DR13 | Steroids, AZA, UDCA, MSM, Antibiotics | Y | Recovery |  |
| Lucas *et al*[37], 2007 | United States | M | 18 | Fecal incontinence, Abdominal Pain | UC | NA | NA | NA | NA | NA | NA |  |
| Protzer *et al*[38], 1996 | Switzerland | M | 22 | Jaundice, Nausea, Diarrhea, Abdominal Pain, Fatigue | UC | PIGCH | SMA | A1, A2, B8, B44, Cw5, Cw7, DR3, DR52, DQ2 | Steroids, UDCA | Y | Recovery |  |
| Protzer *et al*[38], 1996 | Switzerland | F | 32 |  | N | PIGCH | pANCA | A2, A28, B55, B67, Cw3, DR4, DR11, DQ2, DQ3 | Steroids, AZA | Y | Recovery |  |
| Protzer *et al*[38], 1996 | Switzerland | M | 28 |  | N | Cirrhosis, PIGCH | ANA | A1, B8, DR3 | Steroids, AZA | Y | Death |  |
| Protzer *et al*[38], 1996 | Switzerland | M | 26 |  | N | PIGCH | ANA | A1, B8, DR3 | Steroids, UDCA | Y | Recovery |  |
| Hong-Curtis *et al*[39], 2004 | United States | F | 34 | Jaundice, Itching, Fatigue | UC | Anemia | ANA | NA | Steroids, UDCA, Antibiotics | Y | Recovery |  |
| Simão *et al*[40], 2012 | Portugal | M | 15 | Itching | N | None | ANA, AMA | NA | Steroids, AZA, UDCA | Y | Recovery |  |
| Larsen *et al*[41], 2012 | Denmark | M | 10 | Vomiting, Diarrhea, Abdominal Pain, Weight Loss | CD | None | pANCA, SMA | NA | Steroids, AZA, UDCA | N | Recovery |  |
| Guerra *et al*[42], 2016 | Peru | F | 22 | Jaundice, Choluria, Fatigue, Splenomegaly, Ascites | N | Cirrhosis, Esophageal Varices | ANA | A2, A11, B35, B60, DR9, DR13 | Steroids, UDCA | Y | Recovery | Liver transplantation |
| Ng *et al*[43], 2011 | Australia | F | 33 | NA | NA | NA | NA | NA | UDCA | NA | NA |  |
| Igarashi *et al*[44], 2017 | Japan | F | 19 |  | N | None | ANA | NA | Steroids, UDCA | Y | Recovery |  |
| Igarashi *et al*[44], 2017 | Japan | M | 61 |  | N | Renal Cell Carcinoma | NA | NA | Steroids, UDCA | Y | Recovery |  |
| Gargouri *et al*[45], 2013 | Tunisia | M | 10 | Jaundice, Abdominal Pain, Fatigue, Hepatomegaly, Splenomegaly | N | Esophageal Varices | pANCA | NA | Steroids, AZA, UDCA | N | Recovery |  |
| Patrico *et al*[46], 2013 | Italy | F | 7 | Fever, Acholia, Hepatomegaly | N | None | LKM1 | NA | Steroids, AZ | Y | Recovery |  |

M: Male; F: Female; NA: Not available; ND: Not determined, IBD: Inflammatory bowel disease; CD: Crohn’s Disease, UC: Ulcerative Colitis, NSIC: Non Specific Inflammatory Colitis, OS: Overlap syndrome, PSC: Primary sclerosing cholangitis, AIH: Autoimmune hepatitis, PIGCH: Post-infantile Giant Cell Hepatitis, MSM: Mesalamine, SFZ: Sulfasalazine, UDCA: Ursodeoxycholic Acid, AZA: Azathioprine, 6-MP: 6-Mercaptopurine, IFX: Infliximab, ADM: Adalimumab, LKM1: Liver kidney microsome type 1 antibody, AMA: Anti-mitochondrial antibodies, ANA: Antinuclear antibody, SMA: Smooth muscle antibodies, pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies.