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SYSTEMATIC REVIEWS

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

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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

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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 was 3.7%.

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

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 was 3.7%. In conclusion, PSC and AIH overlap syndrome is generally associated with inflammatory bowel disease and has low mortality and good response to treatment.

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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

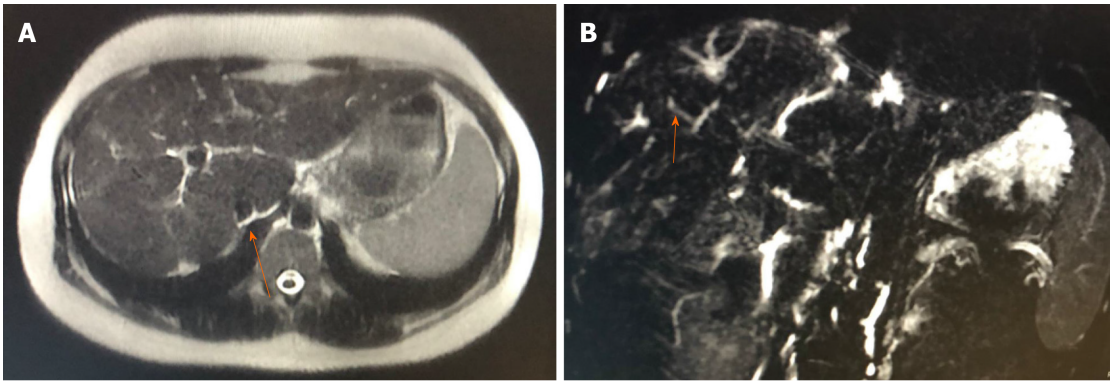

Figure 1 Magnetic resonance cholangiography. A: Reduced-sized liver, with lobulated contours and blunt edges, showing caudate lobe hypertrophy and volumetric reduction of the right lobe periphery; B: Multiple focal areas of caliber reduction in the intrahepatic bile duct, with upstream biliary ectasia,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

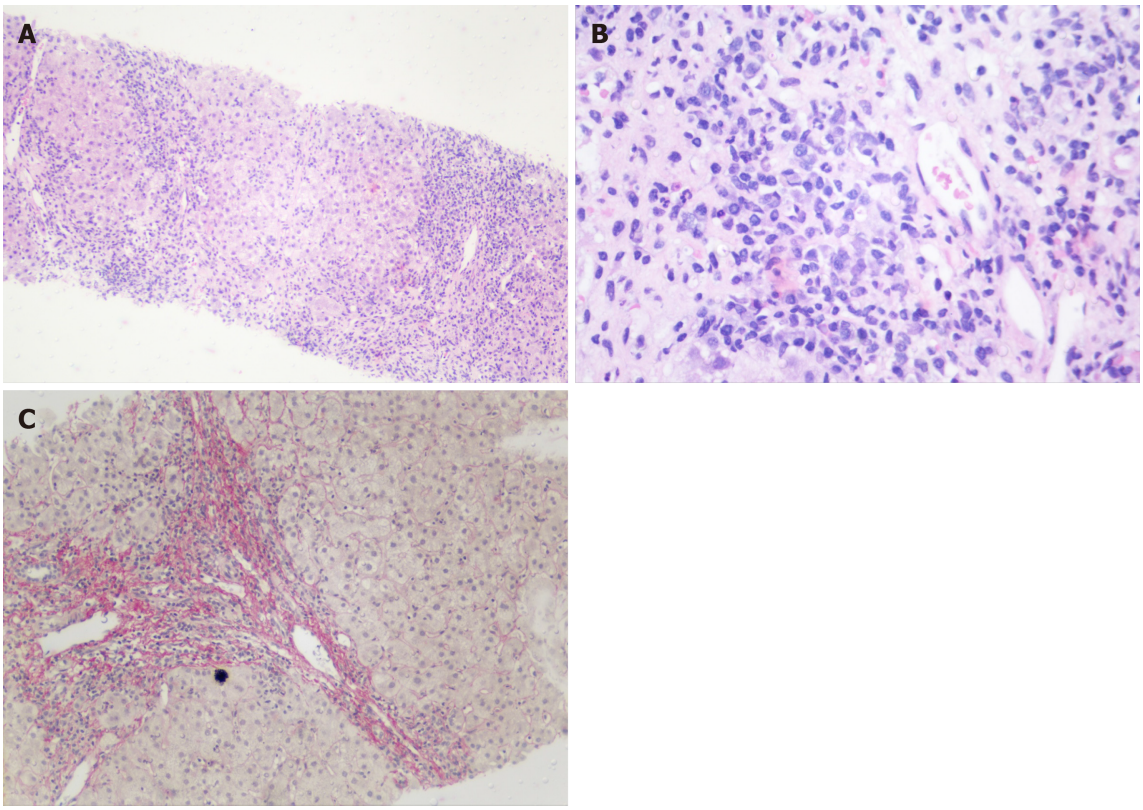

Figure 2 Liver biopsy. A: Intense increase in periportal necroinflammatory activity (Hematoxylin-eosin staining 40 ×); B: Grouping of periportal plasmocyte cells (Hematoxylin-eosin staining 100 ×); and C: Fibrosis in red demarking a nodule (Picro Sirius Red 100 ×).

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.

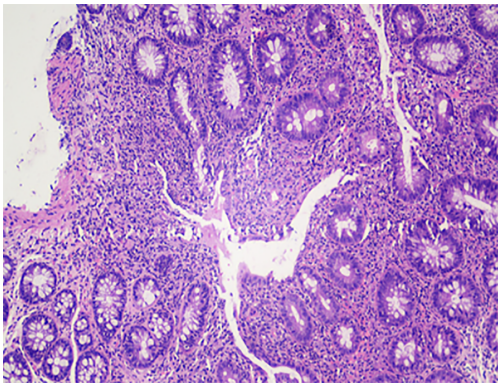

Figure 3 Ascending colon, biopsy. Area of erosion in the ascending colon (Hematoxylin-eosin staining 100 ×).

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

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 (mm^3) (median)	7600
Platelets (mm^3) (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.

(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].

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
Wurbs *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,	Y	Recovery	

								Mycophenolate Mofetil				
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],	Italy	F	16	NA	NA	NA	NA	NA	NA	NA	NA	

2005												
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],	United States	M	18	Fecal incontinence,	UC	NA	NA	NA	NA	NA	NA

2007				Abdominal Pain								
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.

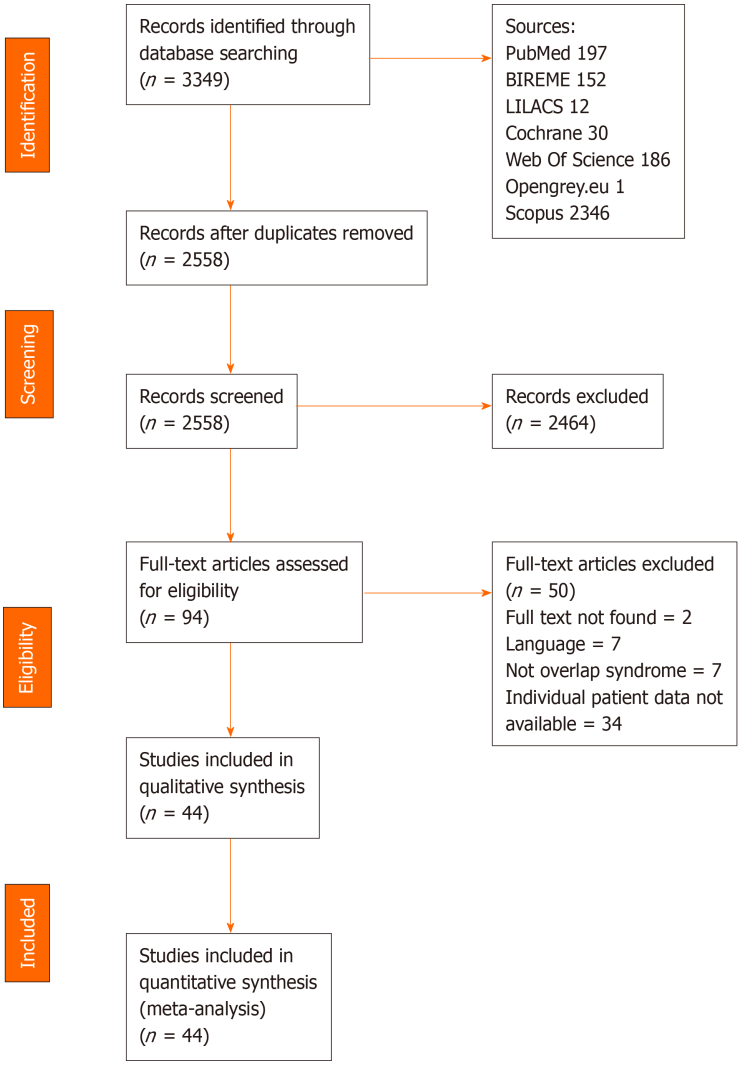

Figure 4 Prisma flowchart.

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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