Cureus
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Open Access Case Report

Seronegative Autoimmune Hepatitis With Primary Biliary Cholangitis Features Presenting As Acute Biliary Disease: A Case Report

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Review began 10/06/2026
Review ended 10/21/2026
Published 10/26/2026

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DOI: 10.7759/cureus.118599

Abstract

Antimitochondrial antibody (AMA) positivity and cholestasis can complicate the distinction between autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC)-AIH overlap. This distinction is particularly difficult during severe acute hepatitis, when cholestasis may accompany hepatocellular injury.

A 69-year-old woman presented with progressive abdominal pain and jaundice. Initial magnetic resonance cholangiopancreatography findings were interpreted as cholecystitis and cholangitis. Persistent hyperbilirubinemia despite antibiotic therapy, together with the absence of biliary obstruction on repeat imaging, prompted investigation for a primary hepatic disorder. The initial alanine aminotransferase (ALT) concentration was 1,522 U/L, and serum immunoglobulin G was 23 g/L during the acute illness. AMA was positive, whereas antinuclear and smooth muscle antibodies were negative; viral hepatitis serology was also negative. Liver biopsy demonstrated severe hepatitis with significant interface activity, multifocal bridging necrosis, and focally prominent plasma cells. Associated canalicular and ductular cholestasis was considered secondary to the hepatic process, and no diagnostic histological features of PBC were identified. These findings supported a working diagnosis of AIH with AMA positivity and cholestatic features, with possible PBC-AIH overlap. Prednisolone was introduced, followed by azathioprine for maintenance immunosuppression. During follow-up, jaundice and pruritus resolved, and ALT and bilirubin normalized. Ursodeoxycholic acid (UDCA), initiated during the diagnostic work-up, was withdrawn after biochemical recovery because of suspected intolerance.

This case illustrates the value of clinicopathological assessment when acute hepatitis presents with biliary imaging abnormalities. Numerical Paris criteria thresholds supported consideration of overlap, but secondary cholestasis and the absence of diagnostic PBC histology limited certainty. AMA-positive AIH remained a plausible alternative.

Categories: Internal Medicine, Gastroenterology
Keywords: autoimmune hepatitis (aih), pbc-aih overlap syndrome, percutaneous liver biopsy, primary biliary cholangitis (pbc), seronegative autoimmune hepatitis, severe hepatitis

Introduction

Autoimmune hepatitis (AIH) is an immune-mediated inflammatory liver disease associated with hepatocellular injury, elevated immunoglobulin G (IgG), and interface hepatitis. Conventional autoantibodies support the diagnosis but may be absent, particularly in acute presentations [1]. Primary biliary cholangitis (PBC) primarily affects the small intrahepatic bile ducts and usually presents with persistent cholestatic liver biochemistry and antimitochondrial antibody (AMA) positivity [2].

AMA positivity alone does not establish PBC or PBC-AIH overlap. AMA can occur in AIH without established PBC, so its significance depends on the biochemical pattern, histology, and subsequent disease course [2,3]. The absence of florid duct lesions or other characteristic biliary injury reduces histological support for PBC, although a negative biopsy cannot exclude early or patchy disease [2].

The Paris criteria support the assessment of PBC-AIH overlap by requiring at least two of three features for each disease component; moderate or severe interface hepatitis is also required in guideline-based application [3,4]. Interpretation is less straightforward during severe acute hepatitis because secondary cholestasis can accompany hepatocellular injury and does not necessarily indicate a separate chronic cholangiopathy [5]. Numerical criteria should therefore be interpreted within the overall clinical and histological context.

We describe an acute hepatitis presentation initially interpreted as biliary disease, in which AMA positivity raised the possibility of PBC-AIH overlap despite biopsy findings favoring a predominant hepatic process.

How to cite this article
Win K, San S, Loitam W, et al. (October 26, 2026) Seronegative Autoimmune Hepatitis With Primary Biliary Cholangitis Features Presenting As Acute Biliary Disease: A Case Report. Cureus 18(10): e118599. DOI 10.7759/cureus.118599

Case Presentation

A 69-year-old woman presented with a three-week history of progressive abdominal pain and new-onset jaundice (day 0). The generalized pain radiated to her back, worsened after eating, and was associated with nausea, anorexia, and unintentional weight loss over one to two weeks. She denied vomiting or fever but described intermittent hot and cold flushes. There was no previous liver disease, recent travel, or family history of liver disease.

Her medical history included ulcerative colitis in long-term remission, chronic obstructive pulmonary disease, and previous ovarian cyst surgery. She had taken mesalazine 1,600 mg twice daily for approximately 30 years, with no dose change before or during the illness. She confirmed no use of over-the-counter medicines, herbal or traditional remedies, vitamins, or supplements before presentation.

On examination, blood pressure was 126/84 mmHg, pulse 79 beats/minute, and oxygen saturation 97% on room air. She was jaundiced, with mild generalized abdominal tenderness and no guarding or peritonism. Initial alanine aminotransferase (ALT) was 1,522 U/L, alkaline phosphatase 185 U/L, and total bilirubin 126 µmol/L. Using the respective upper limits of normal of 40 and 120 U/L, the initial R-ratio was (1,522/40)/(185/120) = 24.7, indicating a predominantly hepatocellular pattern [6]. Selected serial results are presented in Table *1*.

Parameter	Reference interval	Day 0	Day 1	Day 6	Day 10	Day 13	Day 16
ALT (U/L)	0-40	1,522	1,421	897	522	349	221
AST (U/L)	0-40	-	-	-	-	370	-
ALP (U/L)	35-120	185	179	198	173	166	163
GGT (U/L)	1-54	-	-	-	-	403	-
Total bilirubin (µmol/L)	0-21	126	147	308	346	330	322
Albumin (g/L)	34-50	34	33	30	23	24	25
Platelets (×10⁹/L)	150-400	-	-	233	281	308	291
PT (seconds)	10-13.5	-	16.2	16.0	-	-	16.0
INR	0.8-1.4	-	-	-	-	-	1.4

TABLE 1: Selected serial laboratory results during the acute illness

- indicates an unavailable value. Time points refer to selected samples, rather than daily maxima. Acute-episode IgG was 23 g/L (reference interval 6-16 g/L). All numerical results shown precede prednisolone initiation on day 18; the day 16 coagulation results follow vitamin K supplementation begun on day 12. Day 0 denotes the first clinical presentation; all subsequent day numbers indicate elapsed time from that point

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; PT: prothrombin time; INR: international normalized ratio; IgG: immunoglobulin G

Initial magnetic resonance cholangiopancreatography (MRCP) showed diffuse gallbladder wall thickening with minimal pericholecystic fluid, interpreted as acute cholecystitis, and inflammatory change around the porta hepatis and adjacent intrahepatic ducts, suggestive of cholangitis (Figures *1*, *2*; Video *1*). There were no gallstones, ductal calculi, or intrahepatic or extrahepatic biliary dilatation; the common bile duct measured 7 mm.

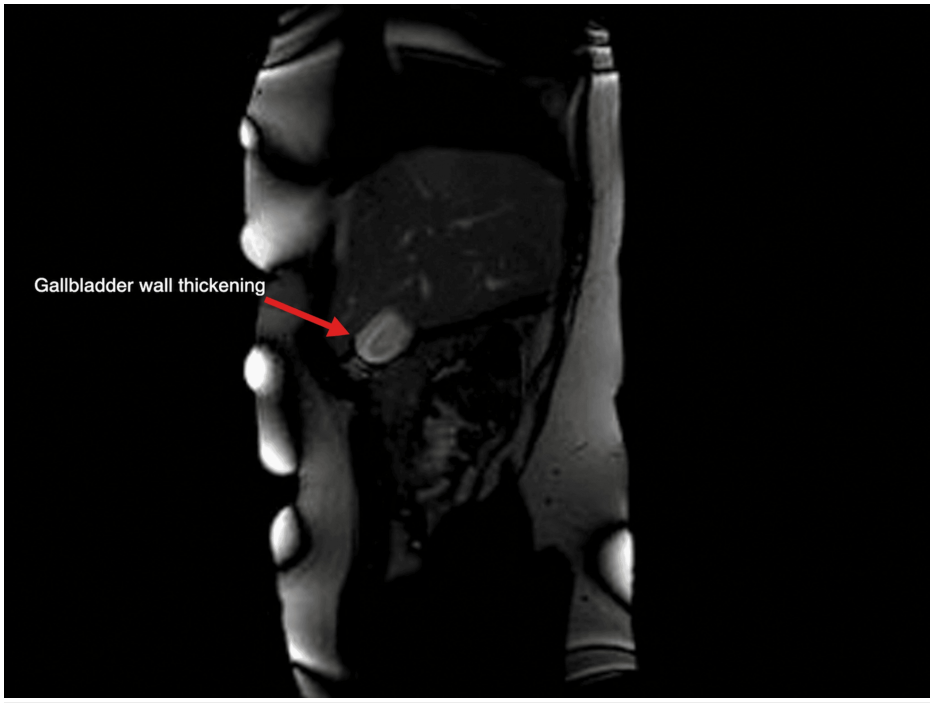


FIGURE 1: Initial MRCP showing gallbladder wall thickening (red arrow), interpreted radiologically as cholecystitis. The full study reported minimal pericholecystic fluid without gallstones or biliary dilatation

MRCP: magnetic resonance cholangiopancreatography

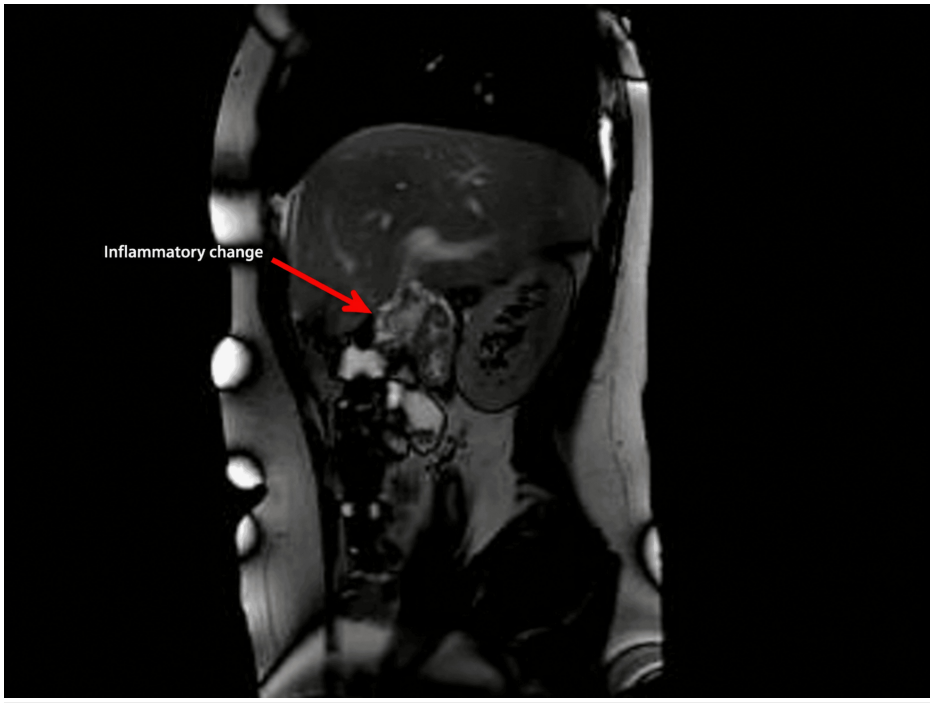


FIGURE 2: Initial MRCP showing inflammatory change in the porta hepatis region (red arrow). The full study described inflammatory changes around the porta hepatis and adjacent intrahepatic ducts, suggestive of cholangitis, without ductal calculi or biliary dilatation

MRCP: magnetic resonance cholangiopancreatography

VIDEO 1: Initial MRCP showing gallbladder wall thickening and inflammatory change in the porta hepatis region

MRCP: magnetic resonance cholangiopancreatography

View video here: https://vimeo.com/1227810417?fl=tl&fe=ec

She received a five-day course of co-amoxiclav from day 0 to day 4. Following discharge, worsening jaundice and persistent anorexia prompted readmission approximately one week later. Intravenous ciprofloxacin and metronidazole were started on day 7 for five days, and trimethoprim on day 10 for five days. Repeat MRCP showed a persistently thick-walled, nondistended gallbladder with pericholecystic fluid, slightly reduced inflammation around the extrahepatic ducts and porta hepatis, and no biliary dilatation or choledocholithiasis (Figure *3*; Video *2*). Small-volume abdominal free fluid and small bilateral pleural effusions were also present. Neither report described multifocal biliary strictures or beading.

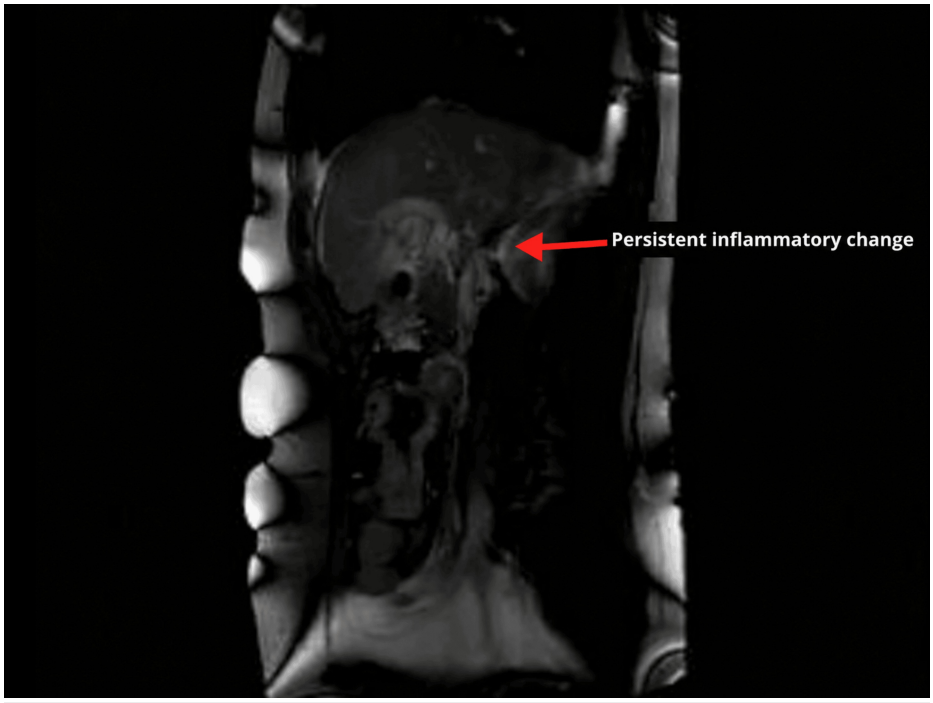


FIGURE 3: Repeat MRCP showing persistent inflammatory change in the porta hepatis region (red arrow). The full report described slightly reduced peribiliary inflammation, persistent extrahepatic duct wall thickening, and no biliary dilatation or choledocholithiasis

MRCP: magnetic resonance cholangiopancreatography

VIDEO 2: Repeat MRCP showing persistent gallbladder wall thickening and peribiliary inflammatory changes

MRCP: magnetic resonance cholangiopancreatography

View video here: https://vimeo.com/1227811070?fl=tl&fe=ec

Bilirubin rose from 126 µmol/L on day 0 to 346 µmol/L on day 10, while ALT fell from 1,522 to 522 U/L over the same interval. By day 16, ALT was 221 U/L, but bilirubin remained 322 µmol/L and albumin 25 g/L. Coagulopathy and mild ascites were noted during the illness. Vitamin K was started on day 12 at 10 mg for three days, followed by 5 mg supplementation; the international normalized ratio was 1.4 on day 16. This early ALT decline preceded corticosteroid treatment.

Autoimmune testing before presentation demonstrated AMA positivity, with negative antinuclear antibodies (ANA) and smooth muscle antibodies (SMA). Serum IgG was 23 g/L during the acute illness (reference interval 6-16 g/L). Hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, and hepatitis E IgM were negative before presentation and again on repeat testing during the acute illness. AMA titer and assay method were not recorded in the available laboratory reports. Elevated cancer antigen 19-9 and alpha-fetoprotein prompted hepatopancreatobiliary multidisciplinary review, but radiological reassessment identified no imaging evidence of cholangiocarcinoma or hepatic malignancy. The documented autoimmune and coeliac investigations are summarized in Table *2*.

Investigation	Result
AMA	Positive
Antinuclear antibodies	Negative
Smooth muscle antibodies	Negative
Gastric parietal cell antibodies	Negative
Tissue transglutaminase IgA antibodies	Negative
Tissue transglutaminase IgG antibodies	Negative
Endomysial IgA antibodies	Negative
Endomysial IgG antibodies	Negative
Serum IgG during the acute illness	23 g/L (reference interval 6-16 g/L)

TABLE 2: Documented autoimmune and coeliac investigations

The autoantibody and coeliac screens were performed before presentation. Earlier serum IgG was 9.5 g/L; the value of 23 g/L was recorded during the acute illness. AMA titer and assay method, anti-LKM1, and anti-SLA/LP results were not documented in the available reports

AMA: antimitochondrial antibody; IgG: immunoglobulin G; IgA: immunoglobulin A; LKM1: liver-kidney microsomal antibody type 1; SLA: soluble liver antigen; LP: liver-pancreas

Ursodeoxycholic acid (UDCA) was started on day 10 at 750 mg in the morning and 500 mg in the evening because of AMA positivity and cholestatic features. Concern for a predominant inflammatory hepatic process led to prednisolone initiation at 30 mg daily on day 18.

Liver biopsy contained approximately 27 portal tracts and showed severe hepatitis with multifocal recent bridging necrosis and significant interface activity (modified hepatic activity index interface component 3). The inflammatory infiltrate included lymphocytes, histiocytes, neutrophils, and focally prominent plasma cells (Figure *4*). Interlobular bile ducts showed degenerative changes, with a significant ductular reaction, canalicular and ductular cholestasis, and rare neutrophils within ductules. There was no granulomatous bile duct destruction or bile duct loss, and no diagnostic histological features of PBC. Cholestasis was considered likely secondary to the hepatic process. Pale collagen within areas of bridging necrosis was interpreted as recent postnecrotic change, with no convincing long-standing fibrosis. The pathological differential included AIH, drug-induced liver injury (DILI), and infection.

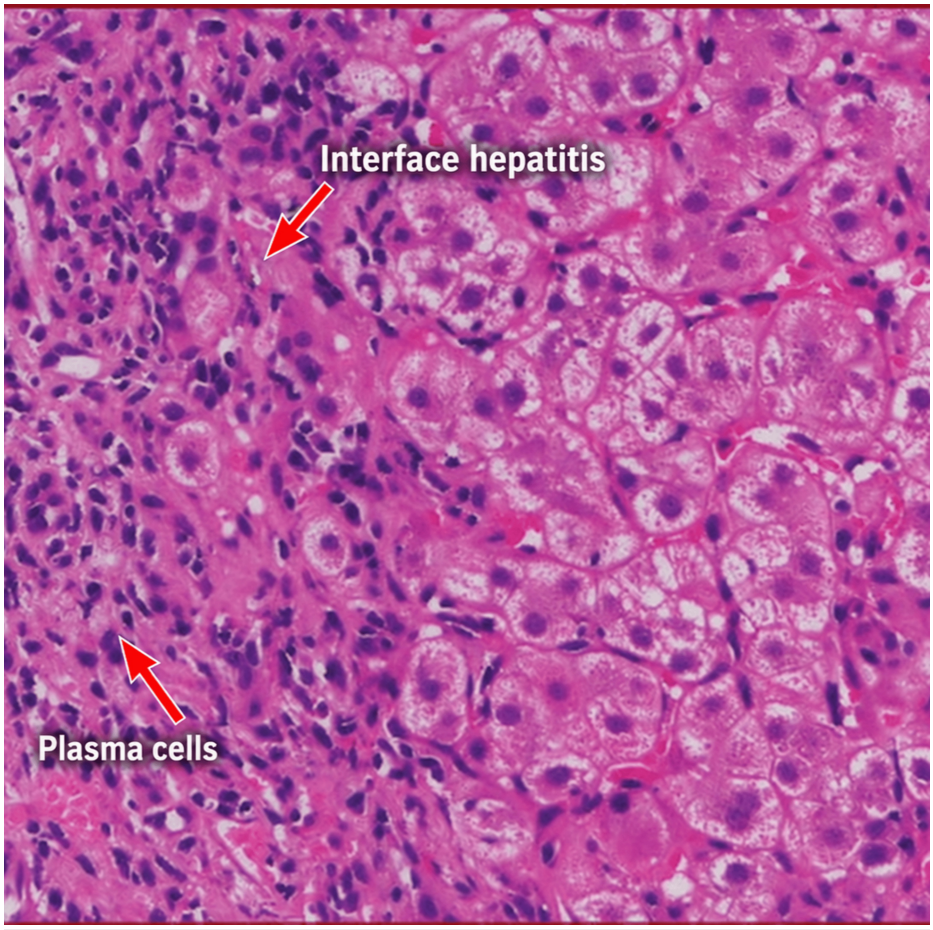


FIGURE 4: Liver biopsy showing interface hepatitis and focally prominent plasma cells (red arrows). The full biopsy assessment demonstrated severe hepatitis with multifocal bridging necrosis and canalicular and ductular cholestasis, considered likely secondary to the hepatic process. No granulomatous bile duct destruction, bile duct loss, or other diagnostic PBC features were identified on the full assessment

PBC: primary biliary cholangitis

The working diagnosis was AIH with AMA positivity and cholestatic features, with possible PBC-AIH overlap. DILI was considered less likely as the primary explanation because symptoms preceded the antibiotic courses and mesalazine had remained unchanged for approximately 30 years. Mesalazine was continued at the same dose during recovery. A contribution from antibiotic exposure to subsequent cholestasis could not be excluded.

Prednisolone was reduced to 20 mg daily on day 25 for two weeks, then to 15 mg daily for one week, followed by 10 mg daily as maintenance treatment. At clinic review on day 61, pruritus had resolved, and azathioprine 75 mg was started for maintenance immunosuppression. By day 75, jaundice had resolved, and ALT and bilirubin had normalized. UDCA was stopped at that review in the setting of abdominal pain, bloating, retrosternal discomfort, and joint pain, raising concern about intolerance. Its withdrawal followed biochemical recovery and was not due to documented biochemical treatment failure. Treatment and follow-up milestones are summarized in Table *3*. During subsequent follow-up, viral PCR testing on day 145 showed no detectable adenovirus, cytomegalovirus, or Epstein-Barr virus DNA.

Time point	Treatment or clinical milestone
Before presentation and throughout illness	Mesalazine 1,600 mg twice daily for approximately 30 years; dose unchanged and treatment continued during recovery
Days 0-4	Co-amoxiclav for five days
Day 7	Intravenous ciprofloxacin and metronidazole commenced for five days
Day 10	Trimethoprim commenced for five days. UDCA commenced at 750 mg each morning and 500 mg each evening. Bilirubin 346 µmol/L
Day 12	Vitamin K commenced at 10 mg for three days, followed by 5 mg supplementation
Day 18	Prednisolone commenced at 30 mg daily
Day 25 onward	Prednisolone reduced to 20 mg daily for two weeks, then 15 mg daily for one week, followed by 10 mg daily maintenance
Day 61	Pruritus had resolved. Azathioprine 75 mg commenced
Day 75	Jaundice had resolved and ALT and bilirubin had normalized. UDCA withdrawn because of suspected intolerance after biochemical recovery

TABLE 3: Treatment and clinical follow-up timeline

Normalization at the day 75 review is reported qualitatively; exact numerical follow-up results were not available

UDCA: ursodeoxycholic acid; ALT: alanine transaminase

Discussion

The principal diagnostic challenge was distinguishing AMA-positive AIH from a PBC-AIH overlap phenotype during a severe acute hepatic illness. Marked ALT elevation, raised IgG, and significant interface hepatitis with focally prominent plasma cells supported the working diagnosis of AIH despite negative ANA and SMA. Negative conventional autoantibodies do not exclude acute AIH [1,5]. The documented results establish ANA/SMA negativity; results for anti-liver-kidney microsomal antibody type 1 or antisoluble liver antigen/liver-pancreas were not available, so a fully characterized seronegative antibody profile could not be claimed.

The initial R-ratio of 24.7 supports a predominantly hepatocellular injury pattern but does not establish its cause [6]. The clinical course also illustrates why falling ALT alone should not be equated with recovery: ALT declined before prednisolone, while bilirubin rose and hypoalbuminemia developed. The later clinical improvement and normalization of ALT and bilirubin occurred during treatment, but exact poststeroid laboratory values and repeat IgG were unavailable. Consequently, the early rate of biochemical response to corticosteroids and formal complete biochemical response could not be quantified.

AMA positivity and the gamma-glutamyl transferase (GGT) elevation raised a reasonable possibility of PBC-AIH overlap. Table *4* applies the Paris criteria to the recorded findings [4]. Two AIH features were present: ALT greater than five times the upper limit of normal and significant interface hepatitis. Two PBC-side thresholds were also reached during the episode: AMA positivity and GGT greater than five times the upper limit of normal. IgG was elevated but below twice the upper limit of normal, and no florid duct lesions were identified.

Disease	Paris criterion	Finding in this patient
AIH	ALT ≥5 × ULN	1,522/40 = 38.1 × ULN on day 0; met
	IgG ≥2 × ULN or SMA positive	IgG 23/16 = 1.44 × ULN; SMA negative; not met
	Moderate or severe interface hepatitis	Significant interface activity, interface component 3; supports this criterion
PBC	ALP ≥2 × ULN or GGT ≥5 × ULN	GGT 403/54 = 7.46 × ULN on day 13; met via GGT. Initial ALP 185/120 = 1.54 × ULN
	AMA positive	Positive; met. Titer and method were not recorded
	Florid bile duct lesions	No diagnostic PBC features; not met

TABLE 4: Patient-specific assessment of the Paris criteria

The criteria require at least two features from each component, with moderate or severe interface hepatitis required in guideline-based application [3,4]. Findings were obtained at different time points during the acute episode; GGT was measured after antibiotic exposure and UDCA initiation. Numerical threshold fulfillment does not resolve whether cholestasis reflects PBC or the acute hepatic process

AIH: autoimmune hepatitis; ALT: alanine transaminase; ULN: upper limit of normal; IgG: immunoglobulin G; SMA: smooth muscle antibodies; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; AMA: antimitochondrial antibody

These numerical findings supported consideration of overlap but did not remove the diagnostic uncertainty. The biochemical results were obtained at different stages of an acute illness, and GGT was measured after both antibiotic exposure and UDCA initiation. Histology favored cholestasis secondary to hepatitis and showed no diagnostic PBC features. Although the absence of characteristic duct lesions does not exclude early or patchy PBC [2], the available evidence supports an AIH-predominant illness with possible overlap rather than definitive PBC-AIH overlap. AMA-positive AIH remains a plausible alternative, and the phenotype may require reassessment during follow-up [3].

Ulcerative colitis also made primary sclerosing cholangitis (PSC) relevant to the differential diagnosis. Neither MRCP report described multifocal strictures or alternating duct narrowing and dilatation, although inflammatory ductal changes were present. The reported imaging did not establish large-duct PSC. The biopsy showed no duct loss or convincing long-standing fibrosis, but the report did not specifically assess periductal fibrosis or fibro-obliterative lesions. Therefore, small-duct PSC could not be conclusively excluded [7].

DILI assessment depended on the exposure chronology. Symptoms preceded co-amoxiclav, ciprofloxacin, metronidazole, and trimethoprim, making these courses unlikely explanations for the onset of hepatitis. Nevertheless, subsequent drug-related cholestasis remained possible. Long-standing unchanged mesalazine use and recovery while it was continued reduced suspicion of mesalazine as the cause. The absence of nonprescribed medicines or supplements narrowed the exposure history, but neither the biopsy pattern nor response during corticosteroid therapy independently excludes DILI or drug-induced autoimmune-like hepatitis [3,6].

Treatment addressed the predominant hepatic process. Corticosteroids were introduced while UDCA was being given, followed by azathioprine for maintenance. Current guidance supports basing variant-syndrome treatment on the dominant clinical and histological component [3]. UDCA withdrawal after recovery because of suspected intolerance should not be interpreted as UDCA nonresponse. Similarly, recovery on immunosuppression supports an immune-mediated hepatitis phenotype but does not independently establish concomitant PBC.

Diagnostic scores require caution in acute hepatitis and suspected variant syndromes [3]. The incompletely documented extended antibody profile and formal histological category limited reliable application of the simplified AIH score.

Conclusions

Severe acute hepatitis may present with gallbladder and peribiliary inflammatory changes that initially suggest biliary disease. In this patient, marked hepatocellular injury, elevated IgG and biopsy evidence of interface hepatitis supported AIH despite negative ANA and SMA. AMA positivity and cholestatic features justified consideration of PBC-AIH overlap, but secondary cholestasis and the absence of diagnostic PBC histology limited certainty. The case is best described as AIH with AMA positivity and possible overlap. Clinical and biochemical recovery occurred during treatment directed at the predominant hepatitis, with continued follow-up needed to clarify the cholestatic phenotype.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Acquisition, analysis, or interpretation of data: Kyaw Wanna Win, Soe Thu Thu San, William Loitam, Myat Lay Khine

Drafting of the manuscript: Kyaw Wanna Win, Soe Thu Thu San, William Loitam, Myat Lay Khine

Critical review of the manuscript for important intellectual content: Kyaw Wanna Win, Soe Thu Thu San, William Loitam, Myat Lay Khine

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors acknowledge using ChatGPT (OpenAI, San Francisco, CA) as an artificial intelligence (AI)-assisted tool during the preparation and editing of this manuscript. The authors reviewed and verified all AI-assisted content and take full responsibility for the accuracy, integrity, and final content of the manuscript.

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