CASE REPORT

Primary biliary cholangitis-autoimmune hepatitis overlap syndrome: an overlapping condition that responded to overlapping treatment

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SUMMARY

Primary biliary cholangitis (PBC) is an autoimmune liver disease, characterised by inflammation and destruction of small bile ducts, leading to cholestasis and eventually biliary cirrhosis. Up to 9.2% of patients demonstrated moderate to severe interface hepatitis, a feature characteristic of autoimmune hepatitis (AIH), hence referred to as PBC-AIH overlap syndrome (PBC-AIH-OS). Here we report a woman in her 50s, presented with severe hepatocellular injury, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 20x upper limit of normal (ULN). Laboratory tests revealed positive anti-mitochondrial antibodies (AMA), anti gp210 and Sp_100 antibodies; raised serum IgG and IgM level, favouring the diagnosis of PBC. However, PBC is more commonly associated with cholestasis rather than hepatocellular injury, hence liver biopsy was performed to look for AIH features which revealed moderate interface hepatitis and confirmed our suspicion of overlap syndrome. Based on the widely used Paris Criteria, she was diagnosed with PBC-AIH-OS and started on treatment promptly. Treatment of PBC-AIH-OS remains controversial with weak recommendation and no clear consensus from the recent guidelines due to the paucity of data. As for our patient, we took a liberal approach and started her on corticosteroids, ursodeoxycholic acid (UDCA) and azathioprine (AZA), a combination of treatments for both PBC and AIH, and she responded well with normalisation of liver enzymes.

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease, characterised by inflammation and destruction of small intralobular bile ducts which leads to cholestasis and eventually biliary cirrhosis. This condition is more prevalent among women in fourth and fifth decades of life with the estimated worldwide incidence and prevalence of 1.76 and 14.6 per 100,000, respectively.[1] The aetiology is not well understood but studies have suggested that environmental and immunogenetic interaction may trigger the pathogenesis of the condition.[2]

Most PBC presents with hepatic inflammation but up to 9.2% of patients demonstrate moderate to severe interface hepatitis, a feature characteristic of autoimmune hepatitis (AIH), hence refer to as PBC-AIH overlap syndrome (PBC-AIH-OS).[3] There is paucity of data on the treatment for PBC-AIH-OS with weak recommendation and no clear consensus based on the recent European Association for the Study of the Liver (EASL) 2017 and Asian Pacific Association for the Study of the Liver (APASL) 2022 guidelines.[4,5] Here we report a case of PBC-AIH-OS which the patient presented with severe hepatocellular injury and responded well to corticosteroids, ursodeoxycholic acid (UDCA) and azathioprine (AZA) combination therapy.

CASE PRESENTATION

A woman in her 50s presented with malaise for 1 month, associated with right hypochondriac pain and jaundice for 4 days. There were no other complaints upon systemic review. She is a social drinker and non-smoker. She denied any use of traditional medications. On physical examination, she was jaundiced, but otherwise unremarkable with normal findings on the abdomen and no stigmata of chronic liver disease.

Initial laboratory tests revealed severe hepatocellular injury with elevated alanine aminotransferase (ALT) 2183 U/L, aspartate aminotransferase (AST) 729 U/L, alkaline phosphatase (ALP) 264 U/L, total bilirubin (TB) 352 umol/L, direct bilirubin (DB) 250 umol/L, of which other possible causes such as viral infection, drug induced and ischaemic hepatitis had been excluded. Iron, serum ceruloplasmin/urinary copper, alpha 1 antitrypsin were normal. Serologic markers showed positive anti-mitochondrial antibody (AMA); negative anti-nuclear antibody (ANA), anti-liver kidney microsome antibody (anti LKM) and anti-smooth muscle antibody (ASMA). Serum IgG and IgM were elevated (Table I). Abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) were done with both reported unremarkable findings of calculous cholecystitis and normal biliary ducts. While positive AMA and elevated serum IgM level favour the diagnosis of PBC, it is not commonly associated with severe hepatocellular injury, hence liver biopsy was performed to look for overlapping AIH features. Meanwhile, her liver function continued to deteriorate in ward as evident by the gradual increase in serum bilirubin level, up to 702 umol/L

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Table I: Initial laboratory test and liver antibodies panel.

Test	Result	RR	Test	Result
Haemoglobin (g/dL)	11.1	11 – 15.2	Anti-HAV IgM	-
White blood cells (10^3/uL)	7.3	4.69 – 12.01	Anti-HAV IgG	+
Platelet (10^3/uL)	328	184 – 432	HbsAg	-
ALT (U/L)	2183	0 – 55	Anti-HbC (Total)	-
AST (U/L)	729	5 – 34	Anti-HCV	-
ALP (U/L)	264	40 – 150	Anti-HIV	-
GGT (U/L)	261	5 – 40	ANA	-
TB (umol/L)	352	3.4 – 20.5	Anti-dsDNA	-
DB (umol/L)	250	0 – 8.6	AMA	+
Albumin (g/L)	31	35 – 50	ASMA	-
INR	1.22		Anti-LKM	-
A1AT (g/L)	2.12	0.9 – 2.0	Anti-gp210	+
Ceruloplasmin (g/L)	0.33	0.16 – 0.45	Anti-Sp100	+
24H urinary copper (umol/24H)	2.56	< 0.9	Anti-Ro-52	-
Ferritin	1043	14 – 233	Anti-SLA/LP	-
IgA (g/L)	2.51	0.65 – 4.21	Anti-LC-1	-
IgG (g/L)	21.76	5.52 – 16.31	Anti-LKM-1	-
IgM (g/L)	4.39	0.33 – 2.93	Anti-PML	-
			Anti-M2-3E	-
			Anti-AMA-M2	-

Initial laboratory results showed markedly elevated transaminases, raised serum bilirubin and negative viral serologies. Raised serum IgG and IgM; positive AMA, anti-gp210 and Sp100 are typically associated with PBC. ALT: alanine aminotransferase; AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, TB: total bilirubin, DB: direct bilirubin, INR: international normalized ratio, A1AT: alpha-1 antitrypsin, HAV: hepatitis A virus, HbsAg: hepatitis B virus surface antigen, anti-HbC (Total): hepatitis B virus core total antibody, HCV: hepatitis C virus, ANA: antinuclear antibody, Anti-dsDNA: anti-double stranded deoxyribonucleic acid antibody, AMA: anti-mitochondrial antibody, ASMA: anti-smooth muscle antibody, Anti-LKM: anti-liver kidney microsome antibody, Anti-gp210: anti-glycoprotein-210 antibody, Anti-SLA/LP: anti-soluble liver antigen/liver-pancreas antibody, Anti LC-1: anti-liver cytosol antibody, Anti-LKM-1: anti-liver kidney microsome 1 antibody, anti-PML: anti-promyelocytic leukemia protein, Anti-AMA-M2: anti-mitochondrial M2 antibody.

and decrease in serum albumin level, down to 23 g/L, both of which are commonly used predictors for short term prognosis of PBC or AIH. Otherwise, her international normalised ratio (INR) was normal and there were no features to suggest hepatic encephalopathy.

Liver biopsy revealed both AIH features with moderate interface hepatitis and portal inflammation with lymphocytes, plasma cells and occasionally eosinophils infiltrates, and PBC features with chronic cholestasis and bile duct paucity (Figure 2A-2F). In addition, she was also noted positive for anti gp210 and Sp_100 antibodies, which are specific for PBC. Based on Paris Criteria, she was diagnosed with PBC-AIH-OS and started on IV hydrocortisone 100 mg BD and UDCA 500 mg/250 mg BD. She responded well to treatment with improvement of liver function and was discharged home with oral prednisolone 1 mg/kg OD, UDCA and outpatient follow up. AZA was added during clinic review, and she was in remission with normalisation of liver function (Figure 1).

DISCUSSION

PBC and AIH are separate clinical entities among autoimmune liver diseases with different biochemical, histological and serological characteristics. Overlapping features between autoimmune liver diseases may present in some patients, which both conditions may occur simultaneously or later in the course of the disease. PBC-AIH is the most common overlap syndrome in this spectrum of diseases.

PBC-AIH-OS is widely defined using the Paris Criteria by fulfilling the following:

At least two out of three features of PBC:

i. ALP > 2x ULN or GGT > 5x ULN.*
ii. AMA positive.*
iii. Florid bile duct lesion on histology.

And at least two of out three features of AIH:

i. ALT > 5x ULN.*
ii. IgG serum levels > 2x ULN or ASMA positive.
iii. Moderate or severe interface hepatitis on histology.*

**Criteria met in our patient*

As per Paris criteria, our patient fulfilled two out of three features of PBC and AIH respectively, establishing the diagnosis of PBC-AIH-OS. It was noted that her serum IgG level was 1.3x ULN which did not meet the Paris Criteria of AIH (> 2x ULN). Studies have debated that serum IgG level seldom raise above 2x ULN which limit the diagnosis of PBC-AIH-OS using Paris Criteria.[6] A study by Wang Q et al in 2013 reported serum IgG levels ≥1.3x ULN has 60% sensitivity and 97% specificity for PBC-AIH-OS, which is more sensitive than Paris Criteria, and also endorsed by the latest APASL guideline.[5,7] At present, there are no clear consensus in regard to the treatment of PBC-AIH-OS due to the paucity of data. EASL 2017 PBC guidelines recommend immunosuppression in patients with severe interface hepatitis and to consider in patients with moderate interface hepatitis.4 Similarly, APASL 2022 PBC guidelines also mentioned that immunosuppression could be used as add-on or de novo combination therapy with UDCA.[5] However, both these guidelines were based on grade III evidence and grade 2

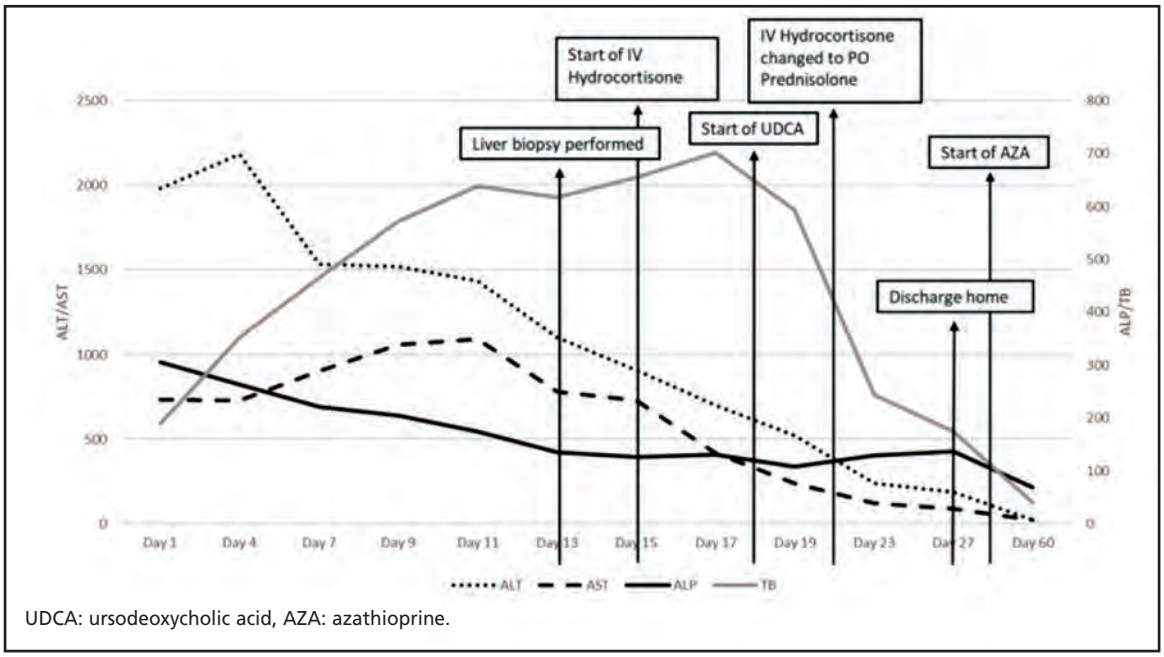

Fig. 1: Liver enzymes (ALT, AST, ALP) and serum bilirubin level over time.

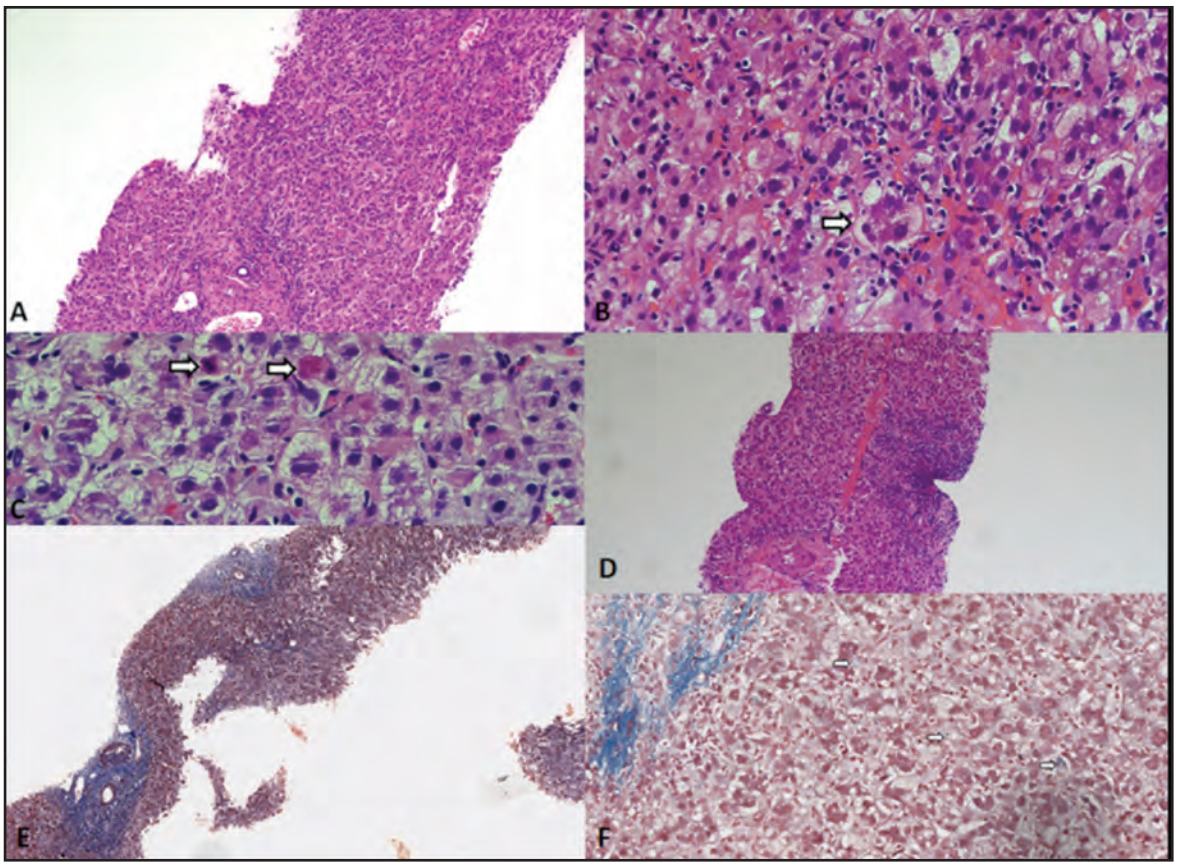

Fig. 2: Photomicrographs of liver biopsy.
A - The liver biopsy shows large portal tract with intact bile duct and mild ductular reaction, interface hepatitis with lymphoplasmacytic infiltrates. The lobules contain scattered foci of spotty necrosis with dropout of hepatocytes. Hepatocanalicular cholestasis is also present. (x10). B - Syncytial giant cell formation in high power view (shown by arrow, x40). C - Scattered acidophil bodies in high power view (shown by arrows, x40). D - Two portal tracts with loss of bile ducts. (x10). E - The figure shows portal fibrosis as highlighted by Masson Trichrome stain (x10). F - The figure shows periportal copper-associated protein as demonstrable by Victoria blue stain (shown by arrows, x40)

recommendation. Meanwhile, American Association for the Study of Liver Diseases (AASLD) 2018 PBC guidelines did not provide recommendation in PBC-AIH-OS, citing no clear consensus on optimal therapy and treatment should be targeted at the predominant histological pattern of injury.[8]

Furthermore, there are conflicting opinions regarding the efficacy of combination therapy (UDCA & immunosuppressive agents). Several studies reported better outcome with combination therapy (UDCA and corticosteroids with or without AZA), as compared to monotherapy alone[9] while the recent meta-analysis by Freedman et al showed no clear differences in clinical outcomes between these treatment regimens.[10]

CONCLUSION

PBC-AIH overlap syndrome (PBC-AIH-OS) is a rare disease but not uncommon among patients with primary biliary cholangitis (PBC). Liver biopsy should be considered if patient with PBC demonstrates autoimmune hepatitis (AIH) features (disproportionately elevated serum transaminases or raised serum IgG level as per PARIS criteria). Treatment of PBC-AIH-OS remains controversial with limited data notwithstanding, we had great result with combination therapy of corticosteroids, ursodeoxycholic acid (UDCA) and azathioprine (AZA) in our patient. Nevertheless, more evidence is still required to provide stronger recommendation and guide the management of such rare disease.

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CONFLICT OF INTEREST

None to declare.

ETHICAL STATEMENT

Verbal consent was obtained from patient for publication of this case report and accompanying images.

REFERENCES

1. Lv T, Chen S, Li M, Zhang D, Kong Y, Jia J. Regional variation and temporal trend of primary biliary cholangitis epidemiology: a systematic review and meta-analysis. J Gastroenterol Hepatol 2021; 36(6): 1423 34.
2. Juran BD, Lazaridis KN. Environmental factors in primary biliary cirrhosis. Semin Liver Dis 2014; 34: 265-72.
3. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011; 54(2): 374-85.
4. Hirschfield GM, Beuers U, Corpechot C, Invernizzi P, Jones D, Marzioni M, et al. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. Journal of Hepatology. 2017; 67(1): 145-72.
5. You H, Ma X, Efe C, Wang G, Jeong S-H, Abe K, Vierling JM, Adams D, Alpini G, et al. APASL clinical practice guidance: the diagnosis and management of patients with primary biliary cholangitis. Hepatol Int 2022; 16(1): 1-23.
6. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D, Vierling JM, David A, Alpini G, et al. The challenges of primary biliary cholangitis: what is new and what needs to be done. J Autoimmun 2019; 105: 102328.
7. Wang Q, Selmi C, Zhou X, Qiu D, Li Z, Miao Q et al. Epigenetic considerations and the clinical reevaluation of the overlap syndrome between primary biliary cirrhosis and autoimmune hepatitis. J Autoimmun 2013; 41: 140-5.
8. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 Practice Guidance from the American Association for the study of liver diseases. Hepatol 2019; 69(1): 394-419.
9. Yang F, Wang Q, Wang Z, Miao Q, Xiao X, Tang R, et al. The natural history and prognosis of primary biliary cirrhosis with clinical features of autoimmune hepatitis. Clin Rev Allergy Immunol 2016; 50(1):114-23.
10. Freedman BL, Danford CJ, Patwardhan V, Bonder A. Treatment of overlap syndromes in autoimmune liver disease: a systematic review and meta-analysis. J Clin Med 2020; 9(5): 1449.