Autoimmune liver disease: evaluating overlapping and cross-over presentations—a case-based discussion

Corrigan, Margaret; Hirschfield, Gideon M

DOI:
10.1136/flgastro-2016-100698

Document Version
Peer reviewed version

Citation for published version (Harvard):
Corrigan, M & Hirschfield, GM 2016, 'Autoimmune liver disease: evaluating overlapping and cross-over presentations—a case-based discussion', *Frontline Gastroenterology*, vol. 7, no. 4, pp. 240-245. https://doi.org/10.1136/flgastro-2016-100698

Frontline Gastroenterology

Autoimmune liver disease: evaluating overlapping and cross-over presentations - a case based discussion

Journal:	*Frontline Gastroenterology*
Manuscript ID	flgastro-2016-100698.R1
Article Type:	Curriculum based clinical reviews
Date Submitted by the Author:	04-May-2016
Complete List of Authors:	Corrigan, Margaret; University of Birmingham, NIHR Liver Biomedical Research Unit; Queen Elizabeth Hospital Birmingham, Liver Medicine Hirschfield, Gideon; University of Birmingham, NIHR Liver Biomedical Research Unit; Queen Elizabeth Hospital Birmingham, Liver Medicine
Keywords:	AUTOIMMUNE BILIARY DISEASE, AUTOIMMUNE HEPATITIS, PRIMARY BILIARY CIRRHOSIS

Autoimmune liver disease: evaluating overlapping and cross-over presentations- a case based discussion

Dr. Margaret Corrigan[1.2] and Dr. Gideon M Hirschfield[1,2]

1. NIHR Birmingham Liver Biomedical Research Unit, University of Birmingham, Birmingham, UK
2. Queen Elizabeth Hospital, Birmingham, UK

Address for Correspondence: Dr. G M Hirschfield, Centre for Liver Research, Institute of Immunology and Immunotherapy, University of Birmingham, Wolfson Drive, B15 2TT. E: g.hirschfield@bham.ac.uk T: 0121 415 8700

Keywords: autoimmune biliary disease, autoimmune hepatitis, primary biliary cirrhosis, primary biliary cholangitis

Word count: 2510

Abstract

The three classic autoimmune liver diseases are recognised based on identifying varying clinical, laboratory, histological and radiological features which collectively classify patients. In the absence of defined aetiological factors it is recognised that disease spectrum is broad, and, in this context, it is not infrequent for disease boundaries to be blurred, leading to overlapping features which may be present at the time of diagnosis, or may appear later in the course of disease. Given the absence of accepted diagnostic criteria for overlap/cross-over syndromes, alongside weak data for intervention, it is recommended that a multi-disciplinary, patient-specific approach is used to establish individual treatment pathways.

INTRODUCTION

Autoimmune liver disease covers a spectrum of uncommon but important liver diseases including primary biliary cirrhosis/cholangitis (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC); each with their own specific classifying criteria (1,2). Whilst most patients meet diagnostic criteria for only one condition, some will have features of more than one condition presenting either simultaneously or sequentially. Such overlap presentations do not reflect distinct disease processes but are better considered as presentations that highlight the breadth of disease manifestation and severity. In those that have a distinct cross-over from one autoimmune liver disease to another, it may be considered as the development of a second autoimmune liver disease in the liver, just as patients with autoimmunity generally are prone to new autoimmune manifestations over time. Given the relatively rare nature of overlap syndromes, and with no randomised data to guide treatment, management of these patients can be challenging. This clinical review addresses competencies laid out in 2E of the 2010 UK Gastroenterology curriculum (Box 1) with a focus on the most common form of overlap (PBC-AIH).

Box 1 – Gastroenterology curriculum 2010 competency

Auto-immune liver disease including autoimmune hepatitis, PBC, PSC and overlap syndromes

- Recognise and appropriately investigate patients
- Appreciate and understand that this range of liver disease is frequently under diagnosed and may have been inappropriately managed
- Select appropriate immunomodulatory therapy, have awareness of side effects, and when they may well require specialist care
- Respond urgently to the management challenge of these severe and often acute diseases and involve more specialist services where required.

BACKGROUND

In their classic description, PBC and AIH are two distinct autoimmune liver diseases, each with their own clinical, biochemical, immunological and histopathological features (Table 1), as well as treatment response. In the majority of cases, distinguishing between a diagnosis of PBC and one of AIH is without strain but for a minority of patients who have features of more than one condition, either at the time of first presentation or over their disease course, the diagnostic process and treatment plan can be challenging. This is a broader reflection that many mechanisms underpinning liver and biliary injury in patients with autoimmune liver disease are shared.

Table 1 - Characteristics of PBC and AIH

	Primary biliary cholangitis/ cirrhosis	Autoimmune hepatitis
Demographics	**Female: male (10:1)** **Typically age >40**	**Female: male (3:1)** **All age groups**
Biochemical profile	**Cholestasis**	**Hepatitic**
Autoantibody profile	**AMA, gp210 sp100, anti-centromere**	**ANA, SMA, anti-F-actin, anti-SLA, anti LKM, anti LC**
Immunoglobulin profile	**IgM**	**IgG**
Biopsy features	**Lymphocytic cholangitis with ductopaenia, granulomas**	**Interface hepatitis, plasma cells**
Treatment	**Ursodeoxycholic acid**	**Immunosuppression**

AMA – anti-mitochondrial antibody, SMA – smooth muscle antibody, LKM – liver kidney microsomal, LC – liver cytosol, SLA soluble liver antigen

DEFINTION OF OVERLAP

Definitions of overlap syndrome are variable and have changed over time as our understanding of autoimmune liver disease has developed. Generally, it is agreed that the presence of a single feature of another condition (for example AMA positivity in a patient with otherwise typical AIH or elevated aminotransferase activity in a patient with classical PBC) is not sufficient to diagnose an overlap syndrome. The stringency of the definitions applied impacts on the reported frequencies of overlap, and additionally reflect the interest and background mechanistic viewpoint of investigators. If investigators believe that therapy with immunosuppression is beneficial then there might be a tendency to apply less stringent definitions, whereas if clinicians see overlap presentations as extreme presentations of one underlying dominant, frequently biliary, process then there may be a reluctance to reach a diagnosis of overlap unless every feature, including response to therapy, is demonstrable for an individual patient.

PREVALENCE

Reported prevalence of PBC-AIH overlap varies depending on definitions used. A commonly used set of classifying criteria derived by Chazouilleres et al (3) identified 12 cases of overlap amongst 130 consecutive patients diagnosed with PBC (9.2%). Czaja (4) applied the IAIHG (International Autoimmune Hepatitis Group) criteria to 37 patients with PBC and found that 7 (19%) satisfied the criteria for AIH. The timing at which such criteria are applied to patients is relevant, as is the appreciation in PBC of a subset of patients with high risk, UDCA non-responsive disease, that might mimic overlap biochemically (5).

PRESENTATION

Patients with overlap syndromes can present in a number of different ways. Some may be identified at the time of diagnosis (the simultaneous presentation), whilst others have a diagnosis of one condition which is stable for a number of years before they develop features of another (the sequential presentation). In those with a simultaneous presentation, extra care needs to be taken when diagnosing overlap as this is most often a reflection of disease variation rather than a true overlap, and many would delay reaching such a diagnosis until after the dominant disease process is treated and a repeat evaluation is undertaken (case 1). The diagnosis in those with a sequential presentation is often much more straightforward and these patients are easier to characterise as having cross-over features. As is characteristic of classical AIH, some patients will have an indolent presentation (case 2) whilst some can have a much more florid presentation (case 3).

DIAGNOSIS

Whilst the presence of a deviation from the normally expected features of a condition should alert the clinician to the fact that a patient may have overlap, the patient should be viewed holistically and no single feature that differs from expected can be used as the sole basis for diagnosis of overlap. The most commonly used criteria in suspected PBC-AIH overlap was developed by Chazouillieres et al (3) (Table 2). Using these criteria, a diagnosis of overlap is proposed if a patient has two out of the three features of PBC as well as two out of three features of AIH. These criteria combine biochemical, immunological and histological features with biopsy being a mandatory requirement. Perhaps in a reflection of

an absent gold standard, these criteria are reported as having a high sensitivity (92%) and specificity (97%) for PBC-AIH overlap (6).

Table 2: Classifying criteria for PBC-AIH overlap

PBC features **ALP >2 x ULN or GGT >5 x ULN** **AMA ≥ 1:40** **Liver biopsy showing florid duct lesions***
And
AIH features **ALT >5 x ULN** **IgG >2 x ULN or positive smooth muscle antibody** **Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis***

*histology is mandatory to classify PBC-AIH in this way

The role of autoantibodies

Establishing the autoantibody profile in patients with autoimmune liver disease is useful in diagnosis and carries a prognostic role helping to establish the disease phenotype, risk of progression and in some cases response to treatment. They can cause additional confusion

for example when a patient with otherwise classical PBC is found to have a positive anti SMA. Again, a holistic view of the patient and clinical scenarios is essential. PBC specific antinuclear antibodies can be useful where there is diagnostic doubt (i.e. AMA negative disease) with anti-Sp100 and anti-gp210 having a high specificity for PBC (>95%). In addition, Nakamura et al (7) demonstrated that anti-gp210 positivity was an independent risk factor for progressive disease (including end stage hepatic failure, hepatocellular carcinoma and variceal bleeding) and liver transplant and that biopsies from these patients typically showed severe interface hepatitis and lobular inflammation. This phenotype can often be confused for PBC-AIH overlap. However, gp210 positivity is a marker of a poor response to steroids (8). The significance of anti sp100 positivity is less well understood but is also thought to be associated with more rapidly progressive disease (9).

TREATMENT

Whilst PBC and AIH both fall under the umbrella term of autoimmune liver disease, their treatment strategies are distinct. Currently, ursodeoxycholic acid (UDCA) is the only treatment licensed for use in PBC (where it is given at a dose of 13-15mg/kg/day), and the mainstay of treatment for AIH is immunosuppression initially with corticosteroids, and subsequently azathioprine. There is a paucity of randomised data to guide treatment guidelines for overlap.

In practice, treatment is commonly guided by the mode of presentation with different strategies employed for those with simultaneous presentations than for those with distinct sequential presentations. In a patient who has overt features of both PBC and AIH at first presentation it is often best to treat with UDCA for six months and then re-evaluate, with

some then considering the addition of corticosteroids if liver biochemical parameters continue to support the presence of a potentially corticosteroid responsive hepatitis. However, the patient demographics are important; we now recognise, for example, that patients diagnosed with PBC before the age of 50, have a high (50%) chance of treatment failure with UDCA, highlighting a more aggressive disease perhaps better considered to be a hepatitic PBC rather than PBC-AIH overlap with the former not responding to steroids.

For a patient with established PBC who subsequently develops features of AIH are offered treatment as per standard AIH guidelines, however with close attention to demonstrating response. Exclusion of drug induced liver injury is important, as is identification of AMA negative PBC. The latter group were classically first described as 'autoimmune cholangitis' precisely because they had elevated IgG values and were AMA negative (10).

WHEN TO REFER FOR SPECIALIST OPINION

Due to the lack of specific diagnostic criteria for overlap, the variety of modes of presentation and the relative rarity of the condition, it can often be difficult to positively or negatively determine the diagnosis of an overlap syndrome. This can lead to under treatment with the risk of uncontrolled disease progressing to fibrosis and cirrhosis or over diagnosis leading to patients receiving escalating immunosuppression and the associated risk of treatment side effects. Referral to a specialist centre with a high volume caseload of patients with autoimmune liver disease should be considered in the following circumstances:

- Patients with UDCA unresponsive disease

- Patients diagnosed with PBC under the age of 50
- Patients with potential overlap where there is diagnostic uncertainty or where immunosuppression is ineffective (ie failure of AST or ALT to fall despite an adequate dose of steroids and azathioprine)

TAKE HOME MESSAGES

- Suspect the diagnosis of overlap in any patient with features of more than one condition either at diagnosis or over the disease course.
- There is no single diagnostic feature for overlap and the patient should be viewed individually, over time, with a focus on the dominant histologic process in particular.
- Be cautious when diagnosing overlap in the young patient with PBC and inflammatory features on biochemistry and histology.
- Liver biopsy, with review by a specialist histopathologist, is essential in the evaluation of overlap presentations.
- If in doubt, refer to a multi-disciplinary expert team for advice.
- Be cognisant that age, gender and ethnicity can impact disease presentation in autoimmune liver disease.

CASE EXAMPLES

Case 1

Miss A presented age 34 with pruritus and cholestatic jaundice (bilirubin 113, ALP 286). Autoantibody screen showed a positive AMA, SMA was negative and IgG was within normal range. She was diagnosed with PBC and commenced on UDCA. After 4 months of treatment with UDCA her ALP remained raised at 379 and her ALT was mildly elevated at 56. She underwent a liver biopsy which showed interface activity and portal inflammation. She was given a diagnosis of overlap syndrome and was commenced on prednisolone but this was stopped after three months. This was followed by a further rise in ALT to 97. As such, prednisolone was restarted and azathioprine added. Despite remaining on prednisolone 20mg and azathioprine being titrated up to 1.5mg/kg/day her ALT remained raised. Her prednisolone was further increased to 30mg and she was referred for tertiary opinion. At this time, she was symptomatic from her steroid use. Her original biopsy was reviewed and whilst it was felt that inflammatory activity was present this could be consistent with biliary disease. Extended serology showed positive ANA 1:100 (multidot pattern), sp100 positive, gp210 negative. The overall impression was that this was not overlap and immunosuppression was withdrawn and UDCA was continued. The patient's biochemistry remained abnormal and she is likely to progress to transplant unless new therapies emerge.

Learning points: this case illustrates a young patient who met diagnostic criteria for PBC but with some features that are inconsistent with classic PBC. It is recognised that patients diagnosed with PBC before the age of 50 have a 50% chance of being UDCA treatment non-responders and that non-response is frequently characterised on the basis of elevated serum aminotransferase activity (11). These patients, sometimes referred to as hepatitic

variant PBC, often have features that suggest overlap syndrome (in this case raised ALT and biopsy features) and differentiating between the two can be complex. In these cases, involvement of a centre with experience of complex autoimmune disease is vital with expert opinion from a specialist hepatologist and histopathologist. Whilst some argue that in such "hepatitic PBC" presentations, with interface hepatitis, that Budesonide has a favourable effect, randomised controlled data to this effect is still lacking. There is, however, emerging evidence for second line therapies for UDCA treatment unresponsive PBC such as the FXR agonist obeticholic acid (12). Whilst this patient was not responsive to UDCA by established criteria, there is no evidence that UDCA should be stopped in these cases and second lines therapies when available are used in addition to rather than instead of UDCA. It is also important to note in this patients that use of immunosuppression is a frequent contra-indication to inclusion in a clinical trial, which therefore means that inappropriate use of immunosuppression may prevent an individual from accessing newer trial based PBC therapies.

Case 2

Mrs. B was diagnosed at the age of 58 with PBC. Extended serology showed AMA positivity (titre 1:100), ANA negative, sp100 and gp210 negative with a normal IgG and raised IgM. She was commenced on treatment with UDCA and her ALP normalised. In 2013 (approximately 6 years after her original diagnosis) she developed symptoms of poor appetite, malaise and diarrhoea. Blood tests performed in primary care showed a predominantly hepatitic picture (Bilirubin 15, ALT 255, AST 150, ALP 106, albumin 42, GGT 74). She underwent a viral screen (negative for CMV, EBV, Hepatitis A, B, C, E) and repeat

immunology (SMA >1:160, IgG 19.04, IgM 7.9). Drug history revealed no culprit medications. Biopsy was consistent with AIH with confluent/bridging necrosis, plasma cells, interface hepatitis and rosettes. She remained on UDCA and was started on prednisolone 20mg with the addition of azathioprine 50mg once biochemical response to steroids was achieved and titrated to a dose of 150mg. The patient achieved normal tests.

Learning points: this case illustrates a consecutive diagnosis of two diagnoses (PBC followed by AIH) which is the most common type of overlap seen in the outpatient setting. Given the time separating the presentations, it is appropriate to investigate the new liver biochemical changes as for any patient; viral screen, drug screen, autoimmune screen. In this case there were clear features of AIH and treatment was commenced as per standard guidelines.

Case 3

Mrs. C had a known diagnosis of PBC and was on treatment with UDCA at a dose of 1000mg daily. In late 2014 she presented for her routine out patient follow up and was found to be jaundiced with grade 1 encephalopathy. The patient reported that she had first noticed the jaundice two weeks prior associated with loose stools and vomiting. There was no history of new medications (either prescribed or over the counter) and no recent travel. Blood tests at presentation showed bilirubin 258, ALT 1211, ALP 141, albumin 28, INR 3.9. Blood tests taken one month prior showed bilirubin 9, ALT 246, ALP 170, INR 1.0, albumin 39. Non invasive liver screen was performed (Hepatitis A, B, C, E, CMV, EBV negative; IgG 25, IgM 11.77, IgA 3.43; AMA positive >1:100, SMA negative, ANA negative, gp210 and sp100 negative). She was commenced on Tazocin and Fluconazole and transferred to her nearest liver transplant centre where she was admitted to critical care due to worsening

encephalopathy. She was placed on the super urgent transplant list and received a donor liver two days later. Explant histology revealed submassive necrosis. Biliary features were present but with mild fibrosis only.

Learning points: A florid presentation of AIH on the background of established PBC is rare. Whilst most will present like case 2, it is important to recognise acute AIH in the context of a patient with underlying PBC and to differentiate from a decompensation of PBC. Management should be as for any patient with acute AIH and liver transplant assessment should be considered. In this case the prior presence of early PBC was not a contraindication to super-urgent registration for transplantation given the distinct clinical presentation of an acute and evolving severe liver injury.

BEST OF FIVE QUESTIONS

Question 1

A 38-year-old female is referred by her GP with abnormal liver biochemistry tests having presented with fatigue and pruritus. She is a smoker with a 10 pack year history and drinks approximately 6-10 units of alcohol per week. Her liver biochemistry shows bilirubin 34, ALT 312, ALP 283, albumin 45, GGT 178. A non invasive liver screen is performed.

Which of these features is not one of the criteria set out by Chazouilleres for the diagnosis of PBC-AIH overlap?

A – AMA titre 1:160
B – ALP 273
C – ALT 312
D – decrease in ALT to 150 and ALP to 130 after 4 months of treatment with UDCA
E – IgG 32.4

Answer: D

This scenario describes a young patient presenting with classical symptoms associated with PBC (fatigue and itch) but a pattern of liver biochemistry that is mixed with both a raised ALP and ALT. Answers A, B, C, E are all elements of Chazouilleres criteria for overlap. The response to UDCA treatment suggests that this is a hepatitic PBC rather than overlap.

Question 2

Mrs. D was diagnosed with PBC at the age of 52 and commenced on UDCA at a dose of 14mg/kg/day. After nine months of treatment her liver biochemistry was entirely normal. She is reviewed in clinic on an annual basis. At a routine follow up she is noted to be

clinically jaundiced. On questioning she reports that she has been off work from her job as a nurse for the last 2 weeks as she felt unwell with joint aches and pains following her returned from holiday in Thailand 3 weeks ago. She was treated for a dental infection two weeks ago. Her blood tests are shown below:

Bilirubin 87, AST 346, ALT 234, ALP 157, albumin 35

AMA 1:160, SMA 1:80, IgG 21

Hb 112, WCC 12.3, platelets 156, MCV 102

Hepatitis B surface antigen negative, hepatitis B surface antibody positive, hepatitis B core antibody negative.

Which of these is the least likely cause of her acute illness?

A. Alcoholic hepatitis
B. Augmentin related liver injury
C. Hepatitis A
D. Immunisation against Hepatitis B
E. PBC/AIH overlap

Answer B:

This scenario describes a patient with established PBC who develops a new onset jaundice with a predominantly hepatitic pattern. All of the above conditions can cause a hepatitic jaundice. AST is higher than ALT and MCV is raised which could suggest alcoholic hepatitis. Given her profession she is likely to have been immunized against hepatitis B which explains the serology. Hepatitis A is a risk given her recent travel. Her blood tests could be consistent with overlap although biopsy is mandatory for the diagnosis. Whilst Augmentin can cause a hepatitic pattern it is more commonly associated with cholestatic jaundice.

Acknowledgements

MC and GH are supported by the NIHR Birmingham Liver Biomedical Research Unit. Opinions expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.

Competing interests

The authors declare no competing interests

REFERENCES:

1. EASL Clinical practice guidelines: Management of cholestatic liver diseases. J Hepatol. 2009; 51: 237-267

2. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WGE, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homber J-C, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RNM, Maddrey WC, Manns MP, Mcfarlane IG, Meyer zum Buschenfelde K-H, Mieli-Vergani G, Yakanuma Y, NIshioka M, Penner E, Porta G, Portmann BC, Reed WD, Rodes J, Schalm SW, Scheuer PJ, Schrumpf E, Seki T, Toda G, Tsuji T, Tygstrup N, Vergani D, Zeniya M. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999; 31: 929-938

3. Chazouillères O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis–autoimmune hepatitis overlap syndrome: Clinical features and response to therapy. Hepatology. 1998;28(2):296–301.

4. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology. 1998: 28; 360-365

5. Trivedi PJ, Corpechot C, Pares A, Hirschfield GM. Risk stratification in autoimmune cholestatic liver diseases: opportunities for clinicians and trialists. Hepatology. 2015; doi: 10.1002/hep.28128

9. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns md, Schrumpf E, on behalf of the International Autoimmune Hepatitis Group. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol. 2011; 54: 374-385

7. Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, et al. Anti-gp201 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007: 45; 118-127

8. Yoshioka Y, Taniai M, Hashimoto E, Haruta I, Shiratori K. Clinical profile of primary biliary

cirrhosis with features of autoimmune hepatitis: importance of corticosteroid therapy. Hepatology Research. 2013: 44; 947-955

9. Czaja AJ. Autoantibodies as prognostic markers in autoimmune liver disease. Digestive Diseases and Sciences. 2010: 55; 2144-2161

10. Michelletti P, Wanless IR, Katz A, Scheuer PJ, Yeaman SJ, Bassendine MF, Palmer JM, Heathcote EJ. Antimitochondrial antibody negative primary biliary cirrhosis: a dIstinct syndrome of autoimmune cholangitis. Gut. 1994; 35(2): 260-265

11. Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, Neuberger JM, Day DB, Ducker SJ; UK PBC Consortium, Sandford RN, Alexander GA, Jones DE. Sex and age are determinants of the clinical phenotype pf primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013; 144(3): 560-569

12. Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, Kowdley KV, Vincent C, Bodhenheimer HC, Pares A, Trauner M, Marschall HU, Adorini L, Sciacca C, Beecher-Jones T, Castelloe E, Bohm O, Shapiro D. Efficacy of obeticholic acid in patients with primary biliary cirrhosis ans inadequate response to ursodeoxycholic acid. Gastroenterology. 2015; 148(4): 751-761