

## Primary biliary cirrhosis in HBV and HCV patients: Clinical characteristics and outcome

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**Author contributions:** Rigopoulou EI, Zachou K and Dalekos GN had the original idea for the study, designed the study protocol and wrote the paper; Zachou K and Gatselis NK did the immune serology and virologic work-up and along with Rigopoulou EI; Papadamou G and Dalekos GN assessed the patients from the immunological and virological points of view; Koukoulis GK did the interpretation of the histological data of the patients; Zachou K, Gatselis NK and Dalekos GN collected the whole data, treated the patients in collaboration with Rigopoulou EI and Papadamou G, and performed the follow-up assessment while contributed to the final version of the paper; Koukoulis GK and Dalekos GN wrote the final version of the paper; all authors have seen and approved the final draft of the paper.

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followed in our center for the presence of concurrent PBC. Seventeen patients identified with concurrent viral hepatitis and PBC (8 HCV and PBC; follow-up:  $61 \pm 37$  mo and 9 HBV and PBC; follow-up:  $57 \pm 38$  mo). PBC diagnosis was established if the patients met at least two of the following criteria: positivity for antimitochondrial antibody, elevated cholestatic enzymes and histological lesions of PBC.

**RESULTS:** HCV or HBV diagnosis preceded that of PBC in most patients by many years. PBC diagnosis was based on the presence of antimitochondrial antibody and elevated cholestatic enzymes in all 17 patients, while one third (5/17; 29.4%) experienced severe pruritus many years before diagnosis. Patients with PBC and HBV were significantly younger at diagnosis of PBC compared to patients with PBC and HCV ( $56.1 \pm 11.2$  vs  $68.5 \pm 10.3$ , respectively,  $P < 0.05$ ). At initial clinical and histological assessment the majority of patients were cirrhotics (10/17; 58.8%) with the group of PBC and HCV carrying the highest frequency (87.5% vs 33.3% in PBC and HBV;  $P < 0.05$ ). The patients with HBV and concomitant PBC seem to have better outcome compared to those with HCV and PBC since none of the 6 non-cirrhotics with HBV and PBC developed cirrhosis during follow-up.

**CONCLUSION:** PBC diagnosis in HBV or HCV patients is very difficult and usually delayed. Therefore, in any case, cholestasis should alert physicians to further search for PBC.

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### Abstract

**AIM:** To present the characteristics, management and outcome of patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections concurrent with primary biliary cirrhosis (PBC).

**METHODS:** Since January 2001 to September 2009, we retrospectively evaluated the medical records of all HBV ( $n = 1493$ ) and HCV patients ( $n = 526$ ) who are

**Key words:** Antimitochondrial antibodies; Autoimmune liver disease; Hepatitis B virus; Hepatitis C virus; Primary biliary cirrhosis.

**Core tip:** In hepatitis B virus (HBV) and hepatitis C virus (HCV) patients the possibility of concomitant primary biliary cirrhosis (PBC), is often very difficult to recognize and therefore, a significant delay in PBC diagnosis in this spe-

cific group of patients is usual. In this report, we clearly show that almost 1% of our HBV and HCV cohort had also PBC which had been misdiagnosed or underestimated for many years. The latter could be the reason of unfavorable outcome observed in our patients and in particular, among HCV/PBC patients. Therefore, the existence of cholestasis should prompt physicians to seek for anti-mitochondrial antibody with various sensitive techniques irrespective of the presence of other liver diseases.

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## INTRODUCTION

Infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) viruses are major public health problems worldwide leading to significant mortality due to hepatic insufficiency and liver cancer<sup>[1,2]</sup>. The prevalence of HBV infection varies considerably among different parts of the world and depends mainly on the age at which infection occurs. Greece is still considered a country with intermediate prevalence for HBV infection<sup>[3,4]</sup>. In the region of Thessaly, central Greece, the prevalence of HBV infection has been estimated to be 4.26% in the general population, while clusters of HBV infection have been recently reported in the same area<sup>[5]</sup>. In contrast, the prevalence of HCV infection is estimated to be low in our area (0.34%), even though clusters of higher HCV prevalence were recently identified by our group<sup>[6]</sup>.

Coexistence, of autoimmune liver diseases like primary biliary cirrhosis (PBC)<sup>[7]</sup> or autoimmune hepatitis (AIH)<sup>[8]</sup> with HCV or HBV infections could be a problem especially in endemic areas for viral hepatitis<sup>[8]</sup>, since viruses in general have long been associated in some cases with the induction of autoimmune phenomena up to the development of overt autoimmune diseases<sup>[8-13]</sup>.

In this context, we have recently described the characteristics of 11 patients with concurrent viral HBV or HCV and AIH alongside with clues to diagnosis, patterns of disease progression and outcome as well as difficulties in decision management<sup>[14]</sup>. Accordingly, the aim of the present study was to explore our data in another autoimmune liver disease namely, PBC by describing the patients' characteristics, management and outcome in patients where HBV and HCV infections concur with PBC since in the current literature there are scarce data to demonstrate the interaction between PBC and viral hepatitis infections.

## MATERIALS AND METHODS

From a total of 1493 patients with chronic HBV and

526 with chronic HCV infection, who attended the outpatient clinic from January 2001 to September 2009, we have retrospectively identified 17 patients with concurrent viral hepatitis and PBC and reviewed their medical records. The demographic and clinical characteristics of these 17 patients along with those of 98 and 303 randomly selected patients from our records with HCV and HBV respectively are shown only in a descriptive way in Table 1 since these groups of HCV and HBV infections without concurrent PBC are not appropriate for statistical comparisons to the HCV or HBV patients and concomitant PBC. All patients were followed at the outpatient clinic of the Department of Medicine, Larissa Medical School, University of Thessaly, Larissa, Greece.

Diagnosis of chronic HCV and HBV infections was based on criteria published in our previous reports<sup>[5,6,15-18]</sup> and according to the consensus statements of the European Association for the Study of the Liver (EASL)<sup>[1,2]</sup>.

Briefly, all HCV patients included in the study met the following criteria: (1) serologic evidence of chronic HCV infection as determined by the detection of antibodies to HCV (anti-HCV) using a second- or third-generation enzyme immunoassay at least twice within 6 mo and (2) active virus replication as defined by the detection of HCV-RNA using a sensitive commercially available quantitative real time PCR kit (COBAS Taqman HCV test; cut-off of detection: 25 IU/mL). All HBV patients included in the study met the following criteria of either chronic hepatitis B such as, (1) serological evidence of chronic HBV infection for at least 6 mo before the entry to the study using commercially available enzyme immunoassays; (2) active virus replication as defined by the detection of HBV-DNA (> 2000 IU/mL), as all patients were HBeAg negative, using a sensitive commercially available quantitative real time PCR kit (COBAS Taqman HBV test; cut-off of detection: 6 IU/mL); (3) persistently or intermittently elevated levels of alanine aminotransferase (ALT) for at least 6 mo before the entry to the study; and (4) histologically proven chronic hepatitis B, or inactive carrier state of HBV infection (HBV positive serology for at least 6 mo but repeatedly undetectable HBV-DNA and normal ALT levels).

According to internationally accepted criteria and to previous publications from our group<sup>[12,19-21]</sup>, patients with PBC met at least two of the following criteria: (1) positivity for anti-mitochondrial antibody (AMA; positive titre  $\geq 1/40$ ) either by IIF on in-house rodent tissue substrates confirmed by Western blot using in-house mitochondrial subfraction of rat livers, or by enhanced performance M2 ELISA (M2 EP (MIT3) ELISA, Quanta Lite, INOVA Diagnostics, San Diego, CA), which was shown to have higher sensitivity compared to the conventional anti-M2<sup>[20,22]</sup>; (2) elevated cholestatic enzymes and (3) histological lesions of PBC (when a liver biopsy had been performed). The presence of other liver diseases and in particular of AIH has been appropriately excluded<sup>[8,23]</sup>.

Response to antiviral treatment in HBV- and HCV-treated patients was assessed according to internationally

**Table 1** Demographic, clinical, laboratory and histological characteristics of hepatitis C or hepatitis B virus patients with concurrent primary biliary cirrhosis or without primary biliary cirrhosis

	PBC+HCV ( <i>n</i> = 8)	PBC+HBV ( <i>n</i> = 9)	<i>P</i> value <sup>2</sup>	HCV ( <i>n</i> = 98)	HBV ( <i>n</i> = 303)
Sex (male/female)	3/5	2/7	NS	62/36	183/120
Age at diagnosis of viral infection (yr)	59.8 ± 13.9	49.9 ± 13.7	NS	44 ± 17	44.4 ± 15.6
Age at diagnosis of primary biliary cirrhosis (yr)	68.5 ± 10.3	56.1 ± 11.2	< 0.05	NA	NA
Age at last follow up (yr)	71 ± 10	60 ± 12	< 0.10	50 ± 12	53 ± 18.3
Diagnosis of viral hepatitis before primary biliary cirrhosis (no/yes)	0/8	2/7	NS	NA	NA
Interval between diagnosis of viral and primary biliary cirrhosis (mo) <sup>3</sup>	106 ± 90	106 ± 89	NS	NA	NA
Source of viral infection	6 unknown, 1 transfusion, 1 <i>i.v.</i> drug use	5 unknown, 2 transfusion, 2 vertical	NS	33 unknown, 22 drug abuse, 32 transfusion, 4 multiple hospitalizations, 3 multiple partners, 1 occupational exposure	9 unknown, 46 sexual, 9 transfusion, 103 vertical, 98 intrafamilial, 38 folk remedies
Active viral infection at diagnosis (no/yes)	0/8	5/4	NS	0/98	187/116
HCV genotype (13 patients with HCV infection)	1b in 3, 3 in 1, undefined in 4	NA	NA	1a/1b in 50, 2a/c in 6, 3a in 27, 4 in 9, 6 undefined	NA
Histology at initial diagnosis (no/yes)	3/5 (4 cirrhosis, 1 moderate fibrosis)	2/7 (1 cirrhosis, 1 pre-cirrhotic, 5 mild fibrosis)	NS	25/73 (18 cirrhosis, 53 mild/moderate fibrosis, 2 severe fibrosis)	202/101 (23 cirrhosis, 78 mild or moderate fibrosis)
Clinically and/or histologically established cirrhosis at initial diagnosis (no/yes)	1/7	6/3	< 0.05	80/18	265/38
Development of cirrhosis during follow up in non-cirrhotic patients (no/yes/NA)	0/1/7	6/0/3	NA	78/2	260/5
Antiviral treatment (no/yes)	4/4	3/6 (2 pre-emptive due to immunosuppression)	NS	0/98	187/116
Type of antiviral treatment	Peg-IFNa plus ribavirin	Nucleos(t)ide analogues	NA	67 IFNa or Peg-IFNa plus ribavirin, 31 IFNa or Peg-IFNa monotherapy	50 IFNa or Peg-IFNa, 56 Nucleos(t)ide analogues
Response to antiviral treatment (no/yes/NA)	2/2/4	0/6/3	NA	39/59/0	45/71/0
Treatment of primary biliary cirrhosis (no/yes)	2/6	5/4	NS	NA	NA
Duration of therapy (mo)	35.8 ± 24.3	73 ± 68	NS	NA	NA
Type of therapy	UDCA	UDCA <sup>1</sup>	NA	NA	NA
Response to therapy at last follow up (no/yes/NA)	(2/4/2)	(2/2/5)	NA	NA	NA
Total follow-up (mo)	61 ± 37	57 ± 38	NS	51 ± 28	75 ± 23
Liver related death (no/yes)	6/2	8/1	NS	98/0	279/24

Results are expressed as mean ± SD, unless otherwise stated. <sup>1</sup>One of them received during the course of the disease also budesonide and later combination of prednisolone with methotrexate due to concomitant CREST syndrome and cryoglobulinemia; <sup>2</sup>Means comparison between primary biliary cirrhosis (PBC) + hepatitis C virus (HCV) and PBC + hepatitis B virus (HBV) groups since comparisons between HCV with (*n* = 8) and without PBC (*n* = 98) as well as between HBV with (*n* = 9) and without PBC (*n* = 303) are not appropriate; <sup>3</sup>Interval between diagnosis of viral and primary biliary cirrhosis was estimated in 15/17 patients, in whom the diagnosis of viral preceded that of autoimmune liver disease (excluded are 2 patients with PBC and HBV infection). NA: Not applicable; NS: Not significant; IFN: interferon; UDCA: Ursodeoxycholic acid (dose: 15 mg/kg per day in two divided doses).

accepted guidelines for the management of HBV and HCV infections<sup>1,2</sup>. Response to UDCA treatment in PBC patients was considered according to the criteria reported by Parés *et al.*<sup>24</sup>.

Thirteen out of 17 patients (76.5%) consented for determination of the human leukocyte antigens (HLA) by polymerase chain reaction-sequence-specific oligonucleotides (PCR-SSO). All liver histology specimens were reviewed by an expert liver immunopathologist (GKK) who was unaware from the status of liver disease of the patients. All subjects consented to participate in the

study at the time of the interview. The ethical committee of the Thessaly University, Medical School approved the study protocol.

### Statistical analysis

Data are presented as mean ± SD or median (range) as appropriate. Data were analyzed by *t* test, the Mann Whitney U test,  $\chi^2$  test (two by two with Yates' correction), or Fisher's exact test, where appropriate using the SPSS 17.0 statistical program. Two sided *P* < 0.05 were considered statistically significant.

**Table 2** Laboratory values at initial and last follow up in the individual groups of patients with viral hepatitis and primary biliary cirrhosis (mean  $\pm$  SD)

Laboratory tests	PBC + HCV (n = 8)	PBC + HBV (n = 9)
Bilirubin initial (mg/dL)	1.0 $\pm$ 0.4	1.8 $\pm$ 1.7
Bilirubin last	4.3 $\pm$ 6.8	2.8 $\pm$ 5.8
Albumin initial (gr/dL)	3.8 $\pm$ 1.0	4.2 $\pm$ 0.7
Albumin last	3.5 $\pm$ 0.8	4.1 $\pm$ 0.7
PT initial (s)	14.5 $\pm$ 4.1	13.6 $\pm$ 1.8
PT last	14.8 $\pm$ 5.2	12.3 $\pm$ 1.4
ALT initial (IU/L)	88 $\pm$ 91	82 $\pm$ 131
ALT last	48 $\pm$ 37	27 $\pm$ 12
AST initial (IU/L)	74 $\pm$ 64	77 $\pm$ 98
AST last	53 $\pm$ 29	42 $\pm$ 38
$\gamma$ GT initial (IU/L)	92 $\pm$ 139	76 $\pm$ 95
$\gamma$ GT last	47 $\pm$ 49	29 $\pm$ 16
ALP initial (IU/L)	100 $\pm$ 29	106 $\pm$ 90
ALP last	93 $\pm$ 35	90 $\pm$ 33
IgG initial (mg/dL)	1764 $\pm$ 470	1815 $\pm$ 762
IgG last	2133 $\pm$ 612	1420 $\pm$ 392
IgM initial (mg/dL)	161 $\pm$ 69	281 $\pm$ 312
IgM last	264 $\pm$ 334	251 $\pm$ 186

PBC: Primary biliary cirrhosis; PT: Prothrombine time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase;  $\gamma$ -GT: Gamma-glutamyl-transpeptidase; ALP: Alkaline phosphatase; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

## RESULTS

### Demographic and clinical characteristics of patients

Eight patients had chronic HCV infection and PBC (follow-up: 61  $\pm$  37 mo) and the remaining 9 had chronic HBV infection and PBC (follow-up: 57  $\pm$  38 mo).

Viral infection had been established in 14 out of 17 patients before their first visit to our clinic. On the contrary, the diagnosis of PBC was established in all but two patients after attending our department. Laboratory data at first and at last follow up visit in our outpatient clinic are presented in Table 2.

The diagnosis of PBC was based on the presence of AMA and elevated cholestatic enzymes in all 17 patients (5 males/12 females), while 5 experienced severe pruritus many years before the diagnosis. A liver biopsy was performed in 12 of 17 patients and had PBC features in 3 of them. In terms of AMA positivity, 14 patients were AMA positive by IIF confirmed by immunoblot, while 3 patients being persistently AMA negative by IIF were found to be repeatedly anti-M2 positive tested by the enhanced performance MIT3-based ELISA and immunoblot<sup>[20,22]</sup>. Two out of 17 patients had also ANA with reactivity against multiple nuclear dots (MND), which is considered specific for PBC<sup>[12,25]</sup>.

### Patients with PBC and HBV infection (n = 9)

Age at first visit to our outpatient clinic was 55  $\pm$  11 years. At the time of diagnosis of HBV infection, the disease was active in 4 patients (range of HBV-DNA: 11.689-773.694 IU/mL). In 7 patients (Table 1), HBV infection was diagnosed before their first visit to our

clinic (median: 67 mo; range 1-168). In these 7 HBV patients, the diagnosis of PBC followed that of HBV (23.5  $\pm$  41.5 mo after their first assessment in the clinic and 106  $\pm$  89 mo after HBV diagnosis), while in the remaining 2 patients, HBV was diagnosed simultaneously in one and 72 mo after the diagnosis of PBC in the other case. Mean Mayo risk score at diagnosis of PBC was 5.7  $\pm$  1.9, while at last follow-up 5.6  $\pm$  2 (mean follow-up: 57  $\pm$  38 mo). HLA typing was available in 7 patients (6 A24 positive, 4 B35 positive, 2 DR1\*14 positive, 1 DRB1\*0401 and 1 DRB1\*0301).

Liver biopsy was performed in 4 patients close to the time of PBC diagnosis (mean time from PBC diagnosis: 1.8 mo), in 2 at the time of PBC diagnosis and in 1 between HBV and PBC diagnosis (biopsy was not done in 2 patients due to coagulation abnormalities; Table 1).

Antiviral treatment with nucleos(t)ide analogues received all patients with active HBV infection (n = 4) with virological response after 1 year of treatment (2 patients received initially lamivudine, while adefovir was added in 1 of them due to virological breakthrough during follow-up; 1 received adefovir and 1 tenofovir). Two out of the remaining 5 patients with inactive disease received also antiviral treatment as preemptive therapy due to chemotherapy and immunosuppression for breast cancer and CREST syndrome accompanied by cryoglobulinemia, respectively.

None of the 6 non-cirrhotic patients developed cirrhosis during the follow-up period. One patient died of liver related causes during the follow-up (decompensated cirrhosis with development of hepatocellular carcinoma).

### Patients with PBC and HCV infection (n = 8)

Age at first visit to the clinic was 66  $\pm$  11 years. HCV infection was active at the time of diagnosis of viral hepatitis in all patients (range of HCV-RNA: 82.894 to more than 850.000 IU/mL). The diagnosis of HCV infection had been established in all but one patient before their first visit to our clinic (median: 114 mo; range: 3-192). HCV genotype was identified in 4 patients (3 patients with 1b and 1 with genotype 3), while in the remaining 4 patients HCV-genotyping revealed undefined results (Table 1). The diagnosis of PBC followed that of HCV in all patients (30  $\pm$  32.1 mo after their first assessment in the clinic and 106  $\pm$  90 mo after HCV diagnosis). Mean Mayo risk score at the time of PBC diagnosis was 6  $\pm$  1.2, while at last follow-up 8.1  $\pm$  3 (mean follow-up: 61  $\pm$  37 mo). HLA typing was available in 6 patients (3 A2 positive, 4 B35 positive, 2 DRB1\*14 positive and 2 DRB1\*13 positive).

Liver biopsy was performed in 2 patients at the time of HCV diagnosis and in 3 after the diagnosis of PBC (mean time from PBC diagnosis 3 mo). However, at the time of the first visit to our clinic, all but one patient had clinically and/or histologically evident cirrhosis (Table 1).

During the follow-up period 4 patients (including 1 with multiple treatment failures in the past) received 48 wk



regiment with Peg-IFN- $\alpha$  and ribavirin with sustained virological response in 2 of them. Reasons for not treating the 4 remaining patients were age older than > 65 years at diagnosis of HCV infection in 3 and psychiatric history in 1 patient.

The only one patient being non-cirrhotic at initial assessment developed histologically proven cirrhosis 168 mo later. Two out of 8 patients died of liver related causes 27 and 57 mo of the follow-up, including 1 patient, who developed hepatocellular carcinoma.

### Comparison between groups

Patients with PBC and HBV were younger at first visit in our clinic compared to patients with PBC and HCV ( $55 \pm 11$  years *vs*  $66 \pm 11$  years;  $P = 0.07$ ). Patients with PBC and HBV were significantly younger at diagnosis of PBC than patients with PBC and HCV ( $P < 0.05$ ) (Table 1). At first assessment 7 of 8 patients (87.5%) with PBC and HCV and 3 of 9 patients (33.3%) with PBC and HBV had clinical evidence of cirrhosis ( $P < 0.05$ ). There were no significant differences concerning the interval between diagnosis of viral hepatitis and PBC and also the total follow-up of the patients.

## DISCUSSION

The present study describes the characteristics of 17 patients with concurrent diagnosis of HBV or HCV infections and PBC alongside with clues to diagnosis, patterns of disease progression, management and outcome. There are several points to be stressed. In the majority of patients the diagnosis of viral hepatitis preceded that of PBC by many years. Several scenarios can be suggested. Autoimmune liver diseases can remain silent for variable period of time before developing symptoms<sup>[7,8,12,19,26]</sup>. Of relevance, viral infections, xenobiotics, drugs and microbes can operate as triggers for the development of liver autoimmunity in genetically predisposed individuals<sup>[7-9,11,12,14,19,25,27,28]</sup>.

In all but two patients with chronic HBV and HCV infections described in our study PBC was diagnosed during the follow-up period for viral hepatitis. The diagnosis of PBC was based in all patients on the presence of elevated cholestatic enzymes and AMA identified either by IIF and immunoblot or by a sensitive MIT3-based ELISA (IgG and IgA) and immunoblot, in those being AMA negative by IIF<sup>[12,19,20,22]</sup>. In addition, ANA specific for PBC, identified in two of these patients, could serve not only as diagnostic tools for PBC but also as prognostic markers of the disease<sup>[12,25,29]</sup>. The detailed work-up for PBC was performed mostly due to persistently elevated cholestatic enzymes during the follow-up period, while intractable pruritus, which is considered a prominent feature of PBC was also evident in almost one third of patients.

These data suggest that existence mostly of biochemical indices of cholestasis should prompt physicians to sick for AMA with various sensitive techniques as well as for PBC-specific ANA irrespective of the presence or

not of other liver diseases<sup>[12,20,22,25,29]</sup>. Since the discovery of AMA, their subsequent inclusion in “routine” auto-antibody testing, has led to PBC being more frequently diagnosed at an earlier stage of disease progression being mainly asymptomatic<sup>[7,12,19,20,25]</sup>. Indeed, up to 60% of PBC patients are reported to be asymptomatic at diagnosis with less severe disease in terms of liver biochemistry and histology compared to symptomatic patients<sup>[7,12,19,20,22,26,30]</sup>.

In accordance with this, the repetitive presence of AMA in our patients, who were mostly asymptomatic, may well signify that PBC was in its early stages. Though, follow-up studies have demonstrated progression of disease in the majority with reduced morbidity and mortality<sup>[31]</sup>. In cases where both cholestasis and pruritus existed long beforehand, the diagnosis of PBC and initiation of UDCA in early stages of the disease could have resulted in significant benefit<sup>[19,24]</sup>. Of note, in patients with viral hepatitis in whom a liver biopsy was available, histological features compatible or typical for PBC were present in 11% of them. This highlights again the importance of careful evaluation of liver biopsy, which in conjunction with laboratory and clinical parameters can help to identify other chronic liver diseases with the potential to independently cause significant morbidity and mortality and/or alter the natural history of the “original” disease. Of relevance, the review of biopsies from 1842 patients with HBV and/or HCV infection from Canada revealed features of other diseases in 20.5% of them, including 3 cases with PBC<sup>[32]</sup>.

The identification of AMA in patients with HCV infection was recently shown to be more frequent than previously thought, reaching up to 8% of the HCV population in a multicenter study from Spain and South America<sup>[33]</sup>. Additionally, in an Italian study, 8% of 170 patients with PBC were found to have HCV infection<sup>[34]</sup>. In these studies coexistence of both diseases might have accelerated the development of cirrhosis and/or neoplasia<sup>[33,34]</sup>. In accordance to this observation, patients with PBC and HCV infection were characterized by significantly higher frequency of cirrhosis compared to our patients with HBV and concomitant PBC. In the whole cohort of patients reported here more than half were cirrhotic at first visit to the clinic, while 17% of them died during a 4 year follow-up period. The big proportion of cirrhosis in this cohort could be potentially ascribed to the presence of two chronic liver diseases, their duration being indeterminate in the majority of them. The fact that diagnosis of PBC was established with delay in the majority of these patients depriving them from beneficial treatment regimens might have also contributed to the progression of liver disease in general. On the other hand however, the potential negative impact of HBV and HCV on the clinical course of PBC cannot be excluded though the number of our case series is adequate for a relatively rare disease like PBC.

In conclusion, our data indicates that chronic viral infections concomitant with PBC are often very difficult to recognize given the heterogeneity of liver diseases,

the absence of awareness of this possibility and the shortfall of many centers outside reference centers to use reliable test for the detection of AMA and/or PBC-specific ANA and enough expertise, including collaboration with histopathologists, for the interpretation of the laboratory results. In other words, the existence mostly of biochemical indices of cholestasis should prompt physicians to sick for AMA and PBC-specific ANA with various sensitive techniques irrespective of the presence of other liver diseases in order to achieve a prompt and rapid diagnosis of concurrent PBC. In addition, we showed that the outcome of patients with viral hepatitis seems to be affected negatively by the concurrent PBC. Although the number of patients in this case study is relatively small, the patients with HBV and concomitant PBC seem to have better outcome compared to those with HCV and PBC probably because of the use of nucleos(t)ide analogues which contrary to IFNs-based treatments in HCV, can control HBV replication with no adjacent effect, related to exacerbation of autoimmune phenomena. The latter finding is also in accordance with our recent report on the better outcome of patients with HBV infection and AIH compared to HCV patients with concurrent AIH<sup>[14]</sup>. Taken together our findings further support the need of close follow-up of at least HCV patients with concomitant autoimmune liver diseases.

## COMMENTS

### Background

Coexistence, of autoimmune liver diseases like primary biliary cirrhosis (PBC) with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections could be a problem especially in endemic areas for viral hepatitis, since viruses in general have long been associated in some cases with the induction of autoimmune phenomena up to the development of overt autoimmune diseases. Therefore, the discrimination between liver autoimmunity and viral liver disease with autoimmune features is mandatory, since these two conditions involve different disease strategies.

### Research frontiers

The characteristics, patterns of disease progression, management and outcome of these patients with HBV and HCV infections concurrent with PBC need to be defined since currently there are scarce data to demonstrate the interaction between PBC and viral hepatitis.

### Innovations and breakthroughs

This is one of the larger series of patients with HBV or HCV infections concomitant with PBC ( $n = 17$ ) ever published. According to the authors' records almost 1% of our HBV and HCV cohort had also PBC which had been misdiagnosed or underestimated for many years. This delay could explain the unfavorable outcome observed in the authors' patients and in particular, among HCV/PBC patients.

### Applications

Chronic viral infections concomitant with PBC are often very difficult to recognize given the heterogeneity of liver diseases, the absence of awareness of this possibility and the shortfall of many centers outside reference centers to use reliable test for the detection of antimitochondrial antibody (AMA) and/or PBC-specific ANA and enough expertise, including collaboration with histopathologists, for the interpretation of the laboratory results. Therefore, existence mostly of biochemical indices of cholestasis should prompt physicians to sick for AMA and PBC-specific ANA with various sensitive techniques irrespective of the presence of other liver diseases in order to achieve a prompt and rapid diagnosis of concurrent PBC.

### Terminology

Concurrent PBC with HBV and HCV is defined as the presence of cholestasis

accompanied by AMA or PBC-specific ANA detection with or without liver biopsy compatible of PBC lesions in patients with well-established chronic HBV or HCV infections.

### Peer review

This is an interesting retrospective analysis of 17 patients with PBC who had in addition infections by HBV or HCV. The study cohort was derived from 1493 patients with HBV infections and 526 patients with HCV infections. The details are well described, the conclusion asks for better evaluations of patients with HBV or HCV infections regarding concomitant PBC.

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