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Is primary biliary cholangitis still a challenge? Experience of Hassan II University Hospital FES Morocco

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Abstract

Introduction: Primary biliary cholangitis is a chronic autoimmune hepatopathy and the leading cause of intrahepatic cholestasis. Treatment is mainly based on ursodesoxycholic acid. The aim of our work is to study the epidemiological, clinical and evolutionary profile of PBC, and to determine the factors predictive of a poor response to UDCA in our context.

Materials and methods: This is a retrospective descriptive and analytical study of all cases of PBC followed in our training program from June 2012 to February 2023.

Results: We recorded all clinical, diagnostic, therapeutic and evolutionary aspects of 70 cases of PBC. Ninety-two percent (n= 65) were women. The mean age was 57.3 [24-83] years. The circumstances of discovery were dominated by pruritus, and jaundice. M2-type anti-mitochondrial antibodies were positive in 91.4% of cases. 52.14% of cases had associated autoimmune diseases. Treatment was based on UDCA in all cases, combined with corticosteroids and immunosuppressants for patients with overlap syndrome. A biochemical response after one year of treatment according to Paris II criteria was found in 62.85% (44 cases). In univariate analysis, the factors associated with poor response to treatment were : Discovery of cirrhosis at diagnosis , Decompensated cirrhosis , presence of overlap syndrome , poor compliance with UDCA due to non-availability of medication , initial bilirubin level above 30 mg/l , hypoalbuminemia below 35 g/l.

Conclusion: Our study shows the frequency of cirrhosis in PBC, which may explain the low response rate to UDCA, a drug that remains difficult to obtain in our Moroccan context, making prognosis poor and management difficult.

Keywords: Primary Biliary Cholangitis; Antimitochondrial Autoantibodies; Overlap Syndrome; Ursodesoxycholic Acid; Cirrhosis

1. Introduction

Primary biliary cholangitis is a cholestatic liver disease, with an autoimmune mechanism that progressively destroys the small and medium intrahepatic bile ducts. It is a rare disease that mainly affects women between the ages of 40 and 60, but can be seen in women of different ages, as well as in men. [1]. In women over 40, the prevalence is 1 in 1000. [1]. The pathogenesis is not yet fully understood, but seems to result from interactions between genetic and environmental factors [2], [3] . PBC is primarily characterized by biological cholestasis, with the presence of anti-mitochondrial M2 antibodies (AMA-M2) leading to the diagnosis.

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The aim of treatment is to prevent progression of liver disease to cirrhosis and its complications [4] . The treatment of choice in PBC remains UDCA at a dose of 13 to 15 mg / kg / day, [5], [6] Access to this drug is difficult, given its unavailability in Morocco.

Evaluation of the biochemical response to UDCA is considered the main prognostic factor. The most widely used definition of biological response is that of Paris II [7] . The aim of our work is to study the clinical and evolutionary profile of PBC, and to determine the factors predictive of a poor response to UDCA in our context.

2. Materials and methods

This is a retrospective descriptive and analytical study of 70 patients with PBC, carried out in our hepato-gastrology department at CHU Hassan II de Fés , Morocco over an 11-year period, from June 2012 to February 2023. All patients with PBC associated or not with autoimmune hepatitis (HAI) were included. Patients with another cause of chronic liver disease, including alcoholic hepatitis, hepatitis B and hepatitis C, were excluded from this study. The medical records of these patients were retrospectively reviewed using currently accepted diagnostic criteria for each disease (**Table I).** We subdivided our patients into 2 groups according to whether or not they had achieved a biochemical response defined according to the Paris II criteria [5] . A univariate analysis was performed to determine whether there were any predictive factors for an incomplete response to UDCA.

Statistical analysis was carried out using SPSS version 26.0 for Windows. Quantitative variables were expressed as mean +/- standard deviation, and qualitative variables as percentage. Univariate analysis was performed using the Chi2 test or Fisher's exact test, with a significance level of $p <= 0.05$.

Table 1 Diagnostic criteria for PBC and HAI [8],[9]

Diagnostic criteria for PBC (at least 2 of the following)	**Diagnostic criteria for HAI (at least 2 of the following three elements)**
Serum PAL ≥2 times ULN and/or GGT ≥5 times ULN	Serum ALT ≥ 5 times ULN
Presence of AMA-M2 at a significant level ≥ 1/40.	IgG level ≥ 2 times ULN or ASMA positive ≥ 1/80
Histologically destructive lymphocytic cholangitis.	Histological evidence of interface hepatitis

AMA-M2: anti-mitochondrial M2 antibody; ASMA: anti-smooth muscle antibody; ALT: alanine transferase test; ULN: upper limit of normal; IgG: immunoglobulin G; PAL: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase.

3. Results

Over a period of 11 years, we collected 70 cases of PBC, with a mean age of 57.3 years[24-83 years]. 92% (n=65) were women, with a sex ratio F/H of : 13 . Mean follow-up was 72 months [12-132 months]. The functional signs noted were: pruritus in (n = 36, 52%) followed by jaundice in (n = 32, 45%), asthenia in (n = 30, 42%), abdominal pain in (n = 12 ,17%) of cases. Biochemically, mean ALAT, ASAT, PAL and GGT levels were 3.09 times the upper limit of normal (ULN) [1-16] ULN, 3.38 [1-23] ULN, 3.74 [2-5] ULN and 5.85 [2-10] ULN respectively. The mean bilirubin level was 46.31[7-48] mg/l .Abdominal ultrasonography during follow-up in all patients showed chronic liver disease in 71.4% (50 cases), steatosis in 4.3% (3 cases) and normal liver in 24.3% (17 cases) .

Table 2 Characteristics of patients with PBC during the study period.

FEATURES	**N (%)**	
Age	20-40 years	6 cases (8.5%)
	40-60 years old	33 cases(48%)
	> 60ans	31 cases (43%)
Gender	Woman	65 cases (92%)
	Men	5 cases (8%)

Average follow-up time	72 months [12- 132]	
Circumstances of Discovery	Asymptomatic	3 cases (4.28%)
	Pruritus	36cas (52%)
	jaundice	32 cases (45%)
	Asthenia	30 cases(42%)
	Abdominal pain	12 cases(17%)
Parameters Biological	Cholestasis	70 cases (100%)
	Hyperbilirubinemia	33 cases (67%)
	Cytolysis	32 cases (45.7%)
	Hypoalbunemia <35g/l	31 cases (44.2%)
	Bilirubin Total >30mg/l	27 cases (38.5%)
AAMs 2 positive	64 cases (91.4%)	
Anti-gp210	3 cases (4.28%)	
Anti sp 100	1 case (1.42%)	
Stage of cirrhosis	Compensated	12 cases (17.14%)
	Decompensated	38 cases (54,28%)

AAMs 2: M2-type anti-mitochondrial antibodies

Table 3 Autoimmune diseases associated with PBC in our study.

Autoimmune diseases	**Number of patients**	**%**
HAI	19	27.14%
Diabetes	9	12.8%
Dysthyroidism	2	2.8%
Rheumatoid arthritis	2	2.8%
Vitiligo	2	2.8%
Sarcoidosis	2	2.8%
Celiac disease	2	2.8%

HAI: autoimmune hepatitis

In our series, 21 patients (30%) underwent liver biopsy. The indication was primarily diagnostic, in the presence of suspected seronegative PBC or overlap syndrome. Histological examination showed liver injury according to Scheuer's classification [10], [11]Stage I in 04 cases (19.04%), stage II in 08 patients (38.09%), stage III in 6 cases (28.57%), stage IV in 3 cases (14.28%) and overlap syndrome in 27.14% (19 cases).

Treatment was based on UDCA in all cases at a dose of 13 to 15 mg/kg/day. Unfortunately, 10 patients (14.28%) were poorly compliant, given the problem of access to treatment in Morocco. In case of overlap syndrome, all patients were put on UDCA at 13 to 15 mg/kg/day combined with corticosteroid therapy and Azathioprine.

A biochemical response after one year's treatment according to Paris II criteria was found in 62.85% of cases. The response to UDCA was incomplete in 37.14% of patients. Among the latter, there were 2 cases (2.85%) associated with dysthyroidism, whose disturbed liver function was completely reversed after management of their dysthyroidism. A combination of fibrates and UDCA was tried in two patients with clinical improvement. Due to its unavailability in Morocco, obeticholic acid was not used. None of our patients underwent liver transplantation. In univariate analysis, the factors associated with poor response to treatment were: discovery of cirrhosis at diagnosis (p=0.005) , decompensated cirrhosis (p=0.006) , presence of overlap syndrome (p=0.01) , poor compliance with UDCA due to

unavailability of the drug (p=0.022), initial bilirubin level above 30 mg/l (p=0.005) , hypoalbuminemia below 35 g/l (p=0.0001) . However, these parameters were not significantly associated with lack of response to UDCA: advanced age at diagnosis, male gender, presence of pruritus, alkaline phosphatase level greater than 3 times normal, Cytolysis outside overlap and syndrome and seronegative form. (Table 4)

Table 4 Predictors of poor response to UDCA in univariate analysis

Variables	**Univariate analysis**
Male sex	p = 1. 00
Advanced age at diagnosis	p= 0.401
Pruritus	p= 0.652
Discovery of cirrhosis at time of diagnosis	p= 0.005
Compensated cirrhosis	p= 0.192
Decompensated cirrhosis	p = 0.006
High initial total bilirubin levels	p= 0.005
High PAL rate	p=0.523
Hypoalbuminemia	p=0.0001
Poor compliance with UDCA	p=0.022
Cytolysis outside overlap syndrome	p=0.097
Overlap syndrome	p=0.01
Seronegative form	p= 0.394

During a mean follow-up period of 72 months [12- 132 months] , the PBC complication rate was 54.28% (n= 38) . Portal hypertension (presence of esophageal varices) and ascites were the most marked complications in our population with 27.14% (n= 19) , 8 ,5% (n= 6) , respectively , followed by digestive hemorrhage and CHC in 5.7% (n= 4) of cases successively , Hepatic encephalopathy in 4.2% (n= 3) and Portal Thrombosis in 2.8% of cases . In our series, death occurred in 7 cases with an estimated prevalence of 10%, all at the stage of decompensated cirrhosis.

Discussion

In our study, primary biliary cholangitis (PBC) affects women in 92% of cases, with a median age at diagnosis of 57.3 years, which is in line with other studies [12], [13]. Only three patients in our series (4.28%) were clinically asymptomatic, and PBC was discovered following investigation of anicteric cholestasis. This finding is in line with observations in the series by Harbi et al. [14]. It is important to note that almost all our patients were symptomatic at the time of diagnosis. Pruritus, jaundice and asthenia were the most frequent signs, found in 52%, 45% and 42% of cases respectively (**Table V).** These observations testify to a delay in diagnosis, which may explain the frequency of cases of inaugural cirrhosis in our study. Indeed, 41,42 % of PBC cases were diagnosed at the cirrhosis stage. This result differs from those reported by H. Jlassi et al. [15] and S. Mrabet [16] who observed frequencies of 46% and 34.6% respectively.

Biologically, cholestasis was found in all our patients and hyperbilirubinemia in 67%.

Associated cytolysis was found in 45.7% of cases. Our results are consistent with the series by S. Bradai et al. [20] and Merzougui et al .[21]

AAMs type 2 is the key test for the diagnosis of PBC, with a sensitivity and specificity of 90% and 97% respectively, according to EASL recommendations. In our series, 91.4% (n= 64 cases) were AAMs type 2 positive, a result comparable with that of European and American studies, which have shown that AAMs positivity is observed in over 90% of PBC patients[6], [22]. Anti-gp210 and anti sp 100 are useful for the diagnosis of PBC in 5-10% of AAM-negative PBC patients [23]-[26],. In our series, anti-gp210 and anti-sp 100 were requested for diagnostic purposes, and led to the diagnosis of PBC in 4 patients (5.71%).

Table 5 Comparison of clinical signs in different series

Series	Pruritus	jaundice	Asthenia
Harbi et al [14]	65.7 %	50.70%	45.71%
Y. Fetati et al [17]	44 %	13.9 %	39.5 %
Hammami et al. [18]	78.8 %	54.92%	45 %
S.Mrabet et al . [16]	28.1 %	-	18.4 %
T. Raja et al. [19]	39.8 %	-	33.3 %
Our series	52%	45%	42%

Liver biopsy is not routinely performed[27], [28], [29], [30]. It isnot useful for diagnosis in cases of typical presentation with elevated PALs On the other hand, it is useful in cases of "seronegative" PBC or suspected HAI. In our population 30% of our patients underwent liver biopsy (PBH) , Scheuer stage II was the most frequent in 38.09%, as described in the literature in the 2 series by S.Mrabet et al . and S. Bradai et al [16], [20] .

Autoimmune disorders are frequently associated with PBC. These systemic manifestations may precede the specific symptomatology of PBC, leading to its discovery. [31]-[40]. The frequency of these associated autoimmune pathologies varies according to the authors from 15 to 84%. In our study, 54.28% (n=38) of our patients had associated autoimmune diseases **(Table 6).** Overlap syndrome (OS) associating PBC and autoimmune hepatitis accounts for 4.3 to 9.2% of PBC and about 8 to 10% of HAI, with variations ranging from 2 to 19% depending on the diagnostic criteria used [41], [42]. In our study, HAI was associated with PBC in 27.14% (19 cases), in line with the work of Hammami et al. in which the association was noted in 28% of cases. [43] .

Table 6 Comparison of autoimmune diseases associated with PBC in different series

Series	HAI(case)	Diabetes	Dysthroidism	Rheumatoid arthritis	Celiac disease	Vitiligo	Sarcoidosis
Dahmani et al [44]	15	4	1	22	2	-	-
S. Bradai et al [20]	5	-	2	2	2	1	-
Gharbi et al[45]	23	11	1	3	2	1	1
Hasnaoui et al[46]	20	7	12	1	1	1	1
Our series	19	9	2	2	2	2	2

The treatment of choice for PBC remains UDCA ; it is prescribed at a dose of 13 to 15 mg/kg/d. [35]A number of studies have demonstrated the value of UDCA in this context [36], [37]Despite the encouraging results of clinical trials, treatment with UDCA has proved difficult in our clinical practice, given its unavailability in Morocco. In our series, a biochemical response after one year of treatment according to the Paris II criteria was found in 62.85% of cases. The response to UDCA was incomplete in 37.14% of patients, a result very close to what is generally described in the literature (Table VII), although it should be noted that 14.28% of patients were noncompliant, given the lack of UDCA in Morocco.

Table 7 Comparison of response to UDCA according to PARIS II criteria in different series

Series	N	Full answer to UDCA	Incomplete response to UDCA
T. Raja et al.[19]	108	49 %	-
H. Jlassi et al. [15]	30	-	47%
S. Mrabet et al .[16]	35	70%	-
S. Bradai [20]	37	35%	-
Our study	70	62.85 %	37.14%

N= number of cases in the series

Treatment of overlap syndrome consists of combining UDCA with the immunosuppressive therapy usually recommended for HAI (corticosteroids and azathioprine). When conventional immunosuppressive agents are ineffective, second-line agents are prescribed, such as cyclosporin, tacrolimus and mycophenolate mofetil [31], [47], [48], [49], [50]In our series, patients diagnosed with overlap syndrome were placed on UDCA with corticosteroid therapy and azathioprine.Complications frequently arise during the course of PBC. Portal hypertension is a common complication. Its prevalence is estimated at between 2.5 and 6% [31]-[50]. It may be responsible for rupture of esophageal varices, ascites or hepatic encephalopathy. HCC is considered a rare complication of PBC.

However, studies are inconsistent, and the exact incidence of HCC in this disease is still poorly understood. Some studies suggest that HCC may be as common in primary biliary cirrhosis as in other causes of cirrhosis [31]-[37].

Table 8 Comparison of PBC complications in different series

Series	Cirrhosis	VO	HDH	EH	Ascites	CHC
Maamouri et al[11]	13.9%	0%	-	-	-	-
Chouqui et al[12].	42.5%	15%	7.3%	15.7%	2.5%	-
Gao et al [56]	50.9%	22%	-	-	-	-
Our series	72.8%	27.14 %	5.7%	4.2%	8 .5%	5.7%

VO: oesophageal varices HDH: upper digestive haemorrhage EH :: Hepatic encephalopathy CHC : hepatocellular carcinoma

Concerning the predictive factors of non-response to UDCA (Table 9) , the results of the univariate analysis showed that advanced age at diagnosis and gender were not significantly associated with an incomplete response to treatment. this is in agreement with the cohort of Cortez-Pinto et al .[52]. the presence of an elevated bilirubin level at the time of diagnosis, as well as the discovery of cirrhosis at the time of diagnosis and the presence of overlap syndrome possibly indicating more severe disease, was associated with a poorer response to treatment , this has been described in the literature [16], [19], [20], [52] Among the possible explanations for this observation is the size of the sample, which may result in insufficient power to detect this difference.

Table 9 Comparison of factors associated with poor response to UDCA in different series

Variables	M,Carbone et al .[51] (n=79)	Cortez-Pinto et al .[52] (n=434)	T. Rajaet al .[19] (n=108)	S. Mrabet et al .[16] (n=35)	S. Bradai et al .[20] (n=37)	Our study (n=70)
Male sex	P < 0.005	p=0.767	-	-	-	p = 1. 00
Advanced age at diagnosis	-	P=0.162	-	-	No correlation	p= 0.401
Discovery of cirrhosis at time of diagnosis	-	p =0.033	p = 0.005	p = 0.04	p = 0.006	p= 0.005

Decompensated cirrhosis	-	-	-	-	-	p = 0.006
High initial total bilirubin levels	-	p=0.014	-	-	p = 0.015	p= 0.005
High PAL rate	-	p =0.013	p = 0.04	-	No correlation	p=0.523
Cytolysis outside overlap syndrome	-	-		p = 0.03	-	p=0.097
Overlap syndrome	-	-	p = 0.002	-	No correlation	p=0.01
Seronegative form	-	-	-	-	No correction	p= 0.394

4. Conclusion

In our study, PBC was discovered at the stage of advanced liver disease in 18.5% of cases, which may explain the low response rate to UDCA, a drug that remains difficult to obtain in our Moroccan context. The association with other autoimmune diseases is very frequent, found in almost half the cases in our series, justifying a systematic search. The discovery of cirrhosis at the time of diagnosis, the existence of decompensated cirrhosis, a high pre- therapeutic total bilirubin level and hypoalbuminemia, and the presence of an overlap syndrome seem to be associated with a poor therapeutic response in PBC in our series.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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