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Primary Biliary Cholangitis in Elderly: About 12 Tunisian Cases

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Abstract

Background and Aims: Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease typically affecting middle-aged women. Older subjects can also be affected. The aim of this study was to analyze retrospectively clinical characteristics and serological markers of PBC in the elderly population.

Methods: It is a retrospective study about 12 elderly patients with PBC diagnosed between 2013 and 2018. All patients had at least two of the three diagnostic criteria of PBC. Data on clinical manifestations and serological tests were recorded. Anti-mitochondrial antibodies (AMA) were determined by indirect immunofluorescence and a line immunoassay was used to determine the reactivity of AMA-M2, M2-3E, gp210 and sp100 antibodies.

Results: Out of 96 patients with PBC, 12 were elderly (12.5%). The sex ratio F/M was 2. The mean age at diagnosis was 72.92 years. The most frequent clinical manifestations at presentation were the fatigue (50%), jaundice (25%) and pruritus (25%). Cirrhosis was present in 58.33% of patients. Ascites, oedemato-ascitic decompensation, portal hypertension, gastrointestinal hemorrhage were present respectively in 25%, 16.67%, 25% and 16.67% of our patients. A cholestasis was present in all the patients. The bilirubin rate was high only in 8.34% of cases. Sixty-six point sixty-seven percent of our patients presented a moderate cytolytic activity. The prevalence of antibody reactivity to anti-AMA-M2, anti-M2-E3, anti-sp100 and anti-gp210 in elderly PBC patients were respectively 90.9%, 100%, 25%, 33.33%.

Conclusion: Greater attention should be given for elderly patients with PBC for the prevention of end-stage liver disease.

Keywords: Primary biliary cholangitis; Elderly; Clinical manifestation;Tunisia

Introduction

Primary biliary cholangitis (PBC) is an autoimmune chronic liver disease, which mainly affected middle-aged women leading to progressive small-sized biliary ducts destruction [1]. According to the European Association for the study of the liver (EASL), the diagnosis is based on the presence of serum liver tests, indicative of a cholestatic hepatitis, in association with circulating anti-mitochondrial antibodies (AMA) or specific antinuclear antibodies (ANA) reactivity, with histologic evidence of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis [2]. The pathogenesis of the diseases is thought to be related to the interaction between genetic predisposition and environmental triggers, which include toxic waste, cigarette smoking, nailpolish, hair dye and various xenobiotic [3].

Bacterial infection has been investigated most intensively, both epidemiologically and experimentally, as a prime environmental etiology in PBC [4]. Furthermore, dysbiosis of the intestinal microbiome can exert profound influence on the bile acid pool and alters the immunological balance of gut liver axis [5]. Jepsen et al. [6] conclude in their review that globally, an estimated 1 in 1,000 women over the age of 40 live with PBC and in the European populations; the estimated incidence is between 1–2 per 100,000 population per year. The disease is predominant in female patients, but some recent studies suggest an increasing male prevalence [2]. Usually, PBC is considered to affect patients aged between 30 and 65 years [7] but it can be diagnosed over 65 years. Older subjects with PBC showed poorer prognosis [8]. Investigations studying PBC confirmed that advanced age had an independent and adverse effect on prognosis, implying that the natural history in the elderly may be worse [9]. However, other studies have shown that PBC is a milder disease in older patients or it is the same disease occurring later in life [10,11]. No data about PBC in elderly was reported in Tunisia. The aim of our study was therefore to analyze retrospectively clinical manifestation and biological markers of PBC in the elderly population in the center of Tunisia.

Materials and Methods

Study population

The study cohort was about 12 PBC patients over 65 years old. All patients had at least 2 of the 3 diagnostic criteria of PBC. The sera were collected between 2013 and 2018 from 3 hospitals in the center of Tunisia. All patients were reviewed retrospectively for demographic characteristics, clinical and laboratory variables. The mean age at diagnosis was 72.92 years. The sex ratio female to male was 2. The study was approved by local Ethics Committee and all patients gave their informed consent.

Methods

Indirect immunofluorescence

Indirect immunofluorescence assay was used as a screening test for AMA detection using a liver, kidney and stomach rat sections (frozen sections of 4 microns thick made in our laboratory) as described previously [12].

Line immunoassays

A multiplexed euroline profile autoimmune liver diseases kit (Euroimmun®, Lübeck, Germany) was used to test all sera. This kit contained the following PBC-associated antigens : the AMA-M2, natively purified from bovine heart containing the E2 subunit of the pyruvate dehydrogenase-complex, the M2-E3, a recombinant fusion protein (BPO) including the immunogenetic domains of the E2 subunits of the branched-chain 2-oxoacid dehydrogenase, (BCOADH) and pyruvate dehydrogenase (PDH) enriched with 2-oxoglutarate dehydrogenase (OGDH), the sp100 (nuclear granular protein), the PML (promyelocytic leukemia protein) and the gp210 recombinant proteins (integral protein of the nuclear membrane). The line immunoassays were performed following the manufacturer's instructions.

Results

Among 96 PBC patients diagnosed between 2013 and 2018, 12 (12.5%) were over 65 years old. There were 8 females and 4 males (sex ratio F/M=2). The mean age at diagnosis was 72.92 years (range 67 to 88 years). Six PBC patients were aged under 70 and 6 were 70 years or older.

The most frequent clinical manifestations at presentation in our elderly patients were the fatigue, jaundice and pruritus found respectively in 50%, 25% and 25%. Only one patient was asymptomatic, the diagnosis of PBC was suspected at the discovery of cholestasis in the biology during a routine review. Cirrhosis is the most important complication of PBC. It was present in 7 patients (58.33%). Ascites, oedemato-ascitic decompensation, portal hypertension, gastrointestinal hemorrhage were present respectively in 25%, 16.67%, 25% and 16.67% of our patients. None patient had hepatic encephalopathy or hepatocellular carcinoma (Tables 1 and 2).

	Patients with PBC (n=12) n (%)
Fatigue	6 (50)
Jaundice	3 (25)
Pruritus	3 (25)
Cirrhosis	7 (58.33)
Ascite	3 (25)
Portal hypertension	3 (25)
Digestive hemorrhage	2 (16.67)
œdemato-ascitic decompensation	2 (16.67)
Asymptomatic (cholestasis)	1 (8.33)

Table 1: Frequency of clinical manifestations and complications of PBC patients.

n	Fatigue	Jaundice	Pruritus	Digestive hemorrhage	Cirrhosis	Ascite	Eodemato-ascitic decompensation	Portal hypertension	Asymptomatic
1		+							
2	+								
3	+		+						
4	+				+	+	+	+	
5	+		+		+	+	+	+	
6		+			+	+			
7	+	+			+			+	
8				+	+				
9				+	+				
10	+								
11			+		+				

12									+

Table 2: Clinical manifestations and complications in 12 elderly patients with PBC.

The biochemical findings showed that gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) were elevated in all the cases. The bilirubin rate was high only in 1 case (9.09%). The rate of platelets was in the physiological limits except one patient who had a slight thrombocytopenia (137000). Prothrombin was less than 70% in 2 cases (22.22%). Concerning transaminases, 8 patients out of 12 (66.67%) presented a mild cytolytic activity not more than twice the upper limit of normal. The prevalence of antibody reactivity to anti-AMA-M2, anti-M2-3E, anti-sp100 and anti-gp210 was respectively 91.67%, 100%, 25% and 33.33% (Tables 3 and 4).

	Patients with PBC (n=12) Mean ratio of result
ALP (x UNL)	3.87 (1.49-8.88)
GGT (x UNL)	6.19 (1.72-12.14)
AST (x UNL)	1.33 (0.40-2.40)
ALT (x UNL)	0.77 (0.30-1.60)
Total bilirubin (mg/dl)	1.31 (0.29-7.12)

Table 3: Biochemical profile of PBC patients; Note: UNL: Upper normal limit, APL: Alkaline phosphatase, GGT: Gamma glutamyl transferase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

The liver biopsy was performed in only two cases. We adopted Scheuer's classification to classify PBC in the patients. The first case was stage 4 Scheuer. The second had mildly active chronic hepatitis.

Three patients had other autoimmune disease associated to PBC: 2 (16.67%) had Hashimoto's thyroiditis and one (8.33%) had autoimmune hemolytic anemia.

All our patients are treated with ursodeoxycholicacid (UDCA).

	Elderly patients with PBC (n=12) n (%)
Elevated APL	12 (100)
Elevated GGT	9 (100)
High total Bilirubin	1 (9.09)
High Transaminases	8 (66.67)
Low Prothrombin (< 70%)	2 (22.22)
Thrombocytopenia	1 (10)
Anti-AMA-M2 antibodies	11 (91.67)
Anti-M2-3E antibodies	12 (100)
Anti-Sp100 antibodies	3 (25)
Anti-gp210 antibodies	4 (33.33)

Table 4: Laboratory data of PBC patients; Note: APL: Alkaline phosphatase, GGT: Gamma glutamyl transferase.

Discussion

In this study, we analyzed the clinical and laboratory data of 12 patients aged over 65 years from a series of 96 patients with PBC. The percentage of elderly in the PBC population was therefore 12.5%, which is similar to that found by Franceschet et al. (16.5%) [13] and Bruguera (16%) [14]. However, this frequency was lower than that of Newton et al. (39%) [15], Hislop et al. (38%) [10], Lehmann et al. (29%) [11] and Muratori et al. (24.75%) [16]. This difference could be due to the fact that in our PBC patients there are more complications than in the other series. In fact, many patients do not consult until they narrowly escape death.

Female predominance was less marked in the patients with older onset PBC than in younger group. In fact, in this study the sex ratio female to male was 2 in elderly patients; however, it was 13 in adult PBC population (data not shown). Our results were different from other series. In fact, Lehman et al. [11], Newton et al. [15] and Franceshet et al. [13] found a sex ratio female to male 6, 8.4 and 7.8 respectively. In another study, all the patients were females [10]. However, our result was similar to that found in the series of Muratori et al. [16] (2 and 1.7 respectively). In fact, some recent data suggest an increasing male prevalence in PBC patients [2,17], probably because cigarette smoking, a habit that concerns more men in our country, contributes to an increased risk of PBC in male [18] and Tunisia ranks first among Arab countries in terms of smoking prevalence among men [19].

EASL recommends the evaluation of all patients for the presence of symptoms, particularly pruritus, sicca complex and fatigue. Whilst end-stage liver disease is associated with progressive symptom burden, severity of symptoms does not necessarily correlate with stage of disease in PBC. The symptoms associated with PBC have a significant impact on quality of life for patients. In this series, fatigue, pruritus and jaundice were the most common signs with a rate of 50%, 25% and 25%, which is similar to what is noted in other series [11,16].

In our study among 12 patients, only one was asymptomatic at presentation. This rate (8.33%) was lower than those found in other series of PBC in the elderly. In fact, the frequency of asymptomatic patients was 31%, 60% and 74% respectively in the studies of Lehmann et al., Newton et al. and Muratori et al. [11,15,16]. However, Hislop et al. [10] found that all the patients over 65 years old were symptomatic.

Regarding the complications, cirrhosis was found in 58.33% of patients. Lehmann et al. found that the frequency of cirrhosis was 37% [11]. The ascites (25%) and gastrointestinal hemorrhage (16.67%) were more common than in series of Lehman et al. [11]. On the contrary, encephalopathy was not encountered in our series comparatively to Lehmann results [11].

In the present study, liver biopsy was performed in only 2 cases (16.67%). In Newton's study, older patients were less likely to have had a confirmed histological diagnosis [15]. EASL recommends evaluating at presentation and during follow up all patients for the stage of disease using non-invasive tests (bilirubin, alkaline phosphatase, aspartate amino transferase, albumin, platelet count, and elastography) [2]. In our series, cholestasis concerned all the elderly patients. ALP was greater than 500 IU/l in 25% of cases, which is similar to that found by Lehmann et al. (30%) [11]. In our study, only one patient (9.09%) had the bilirubin rate more than 50UM/L however it concerns 30% of patients in the study of Lehmann et al. [11]. The mean ratio of ALP, GGT, total bilirubin and AST was higher than that found by Muratori et al.; however, the mean ratio of ALT was lower than Muratori results [16].

More than 60 types of autoantibodies have been detected in PBC patients [20]. Anti-mitochondrial antibodies are considered "the gold marker" for the diagnosis of PBC [21]. A metaanalyse showed that the pooled AMA (all methods) sensitivity and specificity were 84.5% and 97.8%, respectively [22]. Tow subtypes of ANA, anti gp-210 (the nuclear pore membrane glycoprotein 210) and anti-sp100 (the nuclear protein sp100), have been reported to have a high specificity however, their sensitivity was very low. In fact, it has been demonstrated that the sensitivity and specificity of anti-gp210 are 27.2% and 98.5% and the sensitivity and specificity of anti-sp100 antibody are 23.1% and 97.7% [21]. Therefore, ANA directed against gp210 and sp100 can be regarded as additional markers of diagnosis especially in AMA-negative cases. They can also define a subgroup of patients with poor prognosis [23]. In our study, antibodies reactivity to AMA-M2, anti-M2-E3, anti-sp100 and anti-gp210 in elderly PBC patients were 91.67%, 100%, 25% and 33.33% respectively. Muratori et al. [16] found that AMA, immuno-fluorescent staining of nuclear dots (suggesting anti-sp100 reactivity) [2] and perinuclear rims (suggesting anti-gp210 reactivity) [2] were present in 83.67%, 12.24% and 14.28% respectively. This difference between our results could be explained by the fact that we used Euroline immunoassay but Muratori used IIF.

Diseases usually associated with PBC include autoimmune Hashimoto's thyroiditis, Sjögren syndrome, celiac disease and systemic sclerosis [2]. In this study, Hashimoto's thyroiditis was noted in 2 patients (16.7%) and autoimmune hemolytic anemia in one case (8.34%). Lehmann et al. [11] found that autoimmune thyroid diseases, Rheumatoid arthritis, Sjögren syndrome and CREST syndrome were present in 20%, 17%, 14% and 3% respectively. So, systematic screening of autoimmune diseases in PBC patients is needed.

In conclusion, PBC is a rare disease in the elderly (12%). It affects both women and men and it is a serious pathology with a bad prognosis. In fact, more than 50% are already in the cirrhosis stage. Being a symptomatic form in elderly, these patients need attention for the prevention of end-stage liver disease.

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