ORIGINAL INVESTIGATIONS

Autoimmune liver damage in patients with primary Sjogren's syndrome associated with anticentromeric antibodies

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Objective: *to determine the frequency, spectrum and severity of liver affection in anti-centromere antibodies (ACA) positive patients with primary Sjogren's syndrome (pSS).*

Patients and methods. *119 ACA-positive patients with pSS were included in the study, 37 (31%) of them had signs of liver damage, 3 of these patients were excluded from the study (2 had cholelithiasis, 1 had viral hepatitis B). Signs of autoimmune liver damage were found in 34 (28.6%) patients, most of them were seropositive for antimitochondrial antibodies (AMA). The diagnosis of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) was established according to the recommendations of the American Association for the Study of Liver Diseases, the Russian Gastroenterological Association and the Russian Society for the Study of the Liver. In 5 (14.7%) patients the cause of cholestasis remained unspecified.*

Results and discussion. *AMA were found in 73.5% of patients, elevated serum IgM levels – in 57.6%. Clinically liver damage in most cases was characterized by an asymptomatic, slowly progressive course without a dramatic increase of symptoms over time. Liver cirrhosis was found in 14.7% of patients. According to clinical, laboratory and morphological manifestations, PBC was diagnosed in 21 patients, 4 of them also had a cross syndrome with AIH. AMA-negative PBC was found in 3 patients and isolated AIH – in 1. In most cases, histological stage I of PBC was detected. During follow-up, median of 7 years (range from 2 to 15 years), in 7 patients with stage I PBC and in 7 AMA-positive patients without functional liver disorders no clinical, laboratory or instrumental progression of liver damage was noted. In this regard, it was suggested that these patients have epitheliitis of the biliary ducts as manifestation of glandular affection in pSS, and not true PBC.*

Conclusion. *Autoimmune liver lesions are detected in 28.6% of ACA-positive patients with pSS, most (41.2%) of them develop epitheliitis of the biliary ducts as pSS manifestation or a combination of pSS with PBC (with the same frequency), less often PBC / AIH cross syndrome is diagnosed. PBC / pSS-related epitheliitis of the biliary ducts in ACA-positive patients is characterized by a slowly progressive asymptomatic course in most cases and rarely leads to the development of liver cirrhosis.*

Keywords: *anti-centromere antibodies; primary Sjogren's syndrome; systemic sclerosis; primary biliary cholangitis; biliary ducts epiteliitis; autoimmune cholangitis.*

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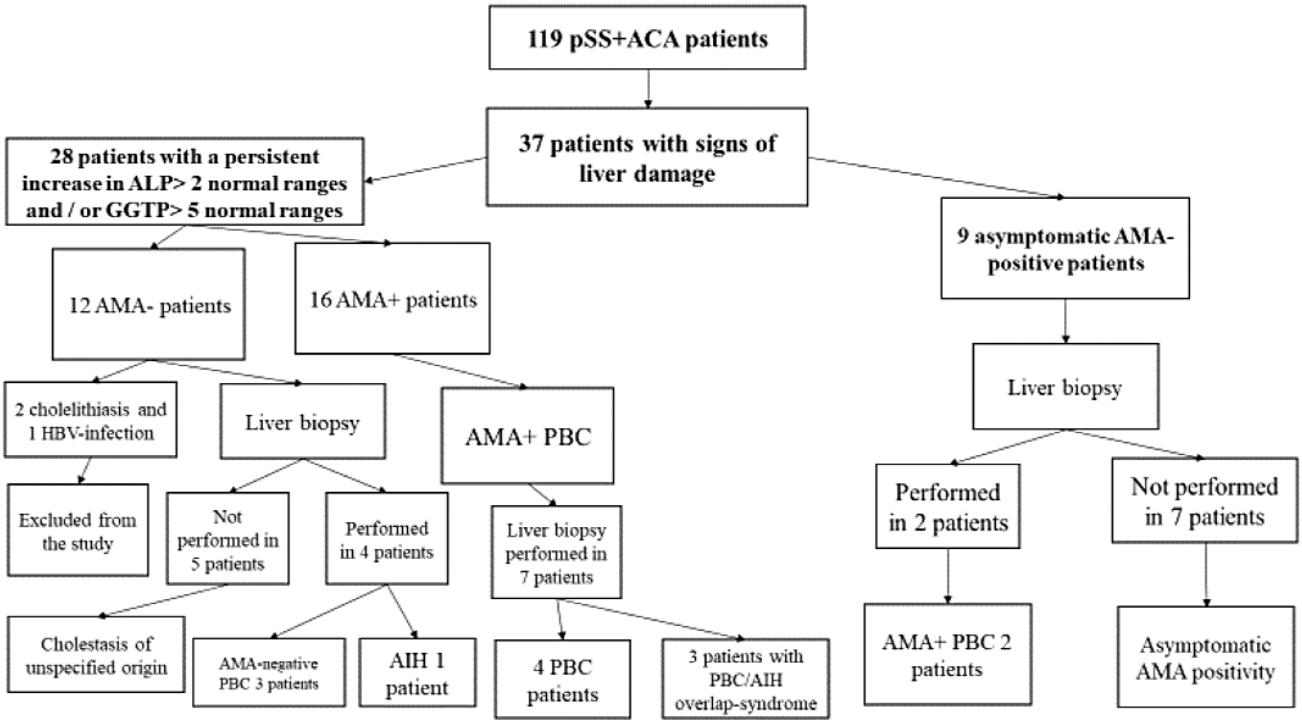
Clinical and biochemical signs of liver damage in primary Sjogren's syndrome (pSS) are found in 5–27% of cases [1–4]. The most common causes of liver damage in patients with pSS are steatohepatitis, drug-induced and viral hepatitis, as well as autoimmune diseases of the liver and biliary ducts [5]. According to a study by M. Kita et al. [6], liver dysfunction was detected in 26.2% of pSS patients and in most cases was associated with the development of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH). It was shown that liver damage was statistically significantly associated with a discrete speckled type of fluorescence of antinuclear factor (ANF) and high titers of anticentromere antibodies (ACAs). This allowed the authors to conclude that patients with pSS and ACA have an increased risk of developing autoimmune liver diseases. Later, this fact was confirmed in other studies [7]. ACAs are often associated with a limited form of systemic sclerosis (SSc) [8, 9], and are also present in 3–27% of pSS patients, causing an increased risk of SSc and autoimmune liver diseases [10, 11]. At the same time, in PBC, these antibodies are often (up to 30% of cases) found in patients without signs of SSc [12–15], especially with low titers or absence of antimitochondrial antibodies (AMA) [13], while AMAs are present in 95 % of patients with PBC [16, 17]. According to some data, the detection of ACA in PBC is regarded as a prognostically favorable marker indicating a milder liver damage compared with ACA-



The frequency and nature of liver damage in ACA-positive pSS patients

negativity [13, 18]; according to others, portal hypertension develops in ACA-positive patients more often [19, 20] and there is a more rapid progression of liver failure [21]. Also, the incidence of Sjogren's syndrome (SS) in patients with PBC varies from 3.5% to 100% [22–30]. It has been shown that when PBC is combined with SS, liver damage occurs in a milder form and progresses more slowly [26, 27, 31]. At the same time, the mortality rate in such patients is higher than in patients with isolated PBC [32]. In previously published studies describing the combination of PBC and SSc, the incidence of SSc in PBC ranged from 1% to 20% [30, 33, 34]. C. Salliot et al. [35] observed a combination with SSc and SS in 40% of PBC patients. According to the Mayo Clinic, 84% of patients with PBC have other autoimmune diseases, of which SSc accounts for 18% [36]. In a Mexican cohort of PBC patients, ACAs were found in 34.5%, while SS was diagnosed in 29.5%, SSc – in 16.6% [16].

The aim of this study is to determine the frequency, spectrum and severity of liver disease in ACA-positive pSS patients.

Patients and methods. The study included 119 ACA-positive pSS patients who met Russian 2001 pSS criteria [37]. ACAs were detected by means of an indirect immunofluorescence reaction using Hep2 cells, as well as using enzyme-linked immunosorbent assay (ELISA, antibodies to CENP-B). All patients underwent standard immunological, dental, ophthalmological and other types of examinations in order to diagnose glandular and extraglandular manifestations of pSS, as well as concomitant rheumatic diseases. Diagnosis of liver damage was carried out based on the assessment of the results of general and biochemical blood tests, coagulogram, detection of AMA-M2 and other markers of autoimmune liver diseases (SLA/LP, ASMA, LKM-1, gp210, sp100) by immunoblot and/or ELISA, as well as morphological study of liver biopsies, which was carried out at the Department of Pathological Anatomy of Sechenov First Moscow State Medical University.

Thirty seven of 119 patients (31%) had signs of liver damage (see figure): 28 (75.7%) – cholestasis according to the biochemical blood test (increased level of alkaline phosphatase [ALP] > 2 normal values and/or gamma-glutamyl transpeptidase [GGTP] > 5 norms); 9 (24.3%) – a significant increase in the level of AMA without changes in the biochemical blood test. The majority of patients (68.9%) had no signs of liver damage.

Of 28 patients with signs of persistent cholestasis, 16 (57.1%) had high AMA levels and, according to the recommendations of the American Association for the Study of Liver Diseases [17], the Russian Gastroenterological Association, and the Russian Society for the Study of the Liver [38], they were diagnosed with PBC. Later, 7 of them underwent liver biopsy in order to clarify the stage of PBC and exclude the overlap-syndrome with AIH. The remaining 12 patients with signs of cholestasis were AMA-negative: 3 of them were excluded from the study – 2 had cholelithiasis and 1 had HBV-infection; 4 patients underwent liver biopsy, according to its results, AMA-negative PBC was established in 3 cases, AIH in 1; in 5 patients the diagnosis was interpreted as cholestasis of unspecified genesis.

Of 9 patients with asymptomatic elevation of AMA levels, two underwent liver biopsy and a diagnosis of PBC was made.

Thus, 37 (31%) of 119 patients were diagnosed with SSc according to ACR / EULAR (American College of Rheumatology/European League Against Rheumatism) 2013 criteria [39]; 34 patients (28.6%) had signs of autoimmune liver damage.

Results. The majority (73.5%) of the patients were AMA-positive, all had high ANF HEp-2 titers, mainly centromeric pattern, and only 6 patients had an antimitochondrial pattern

Table 1. Laboratory abnormalities in ACA-positive pSS patients with autoimmune liver damage

	Number of patients	
Sign	**№**	**%**
AMA (>10 IU/ml)	25/34	73.5
ANF Hep2 (≥1/320)	34/34	100
Hyperglobulinemia (> 18%)	6/34	17.6
High IgG (>16 g/L)	3/33	9
High IgM (>2.5 g/L)	19/33	57.6
High IgA (>4 g/L)	9/33	27.3
High CRP (> 5 mg/L)	5/34	14.7
Anemia (Hb<120 g/L)	4/34	11.8
Leukopenia (< 4 x 10^9 /L)	6/34	17.6
Thrombocytopenia (< 100 x 10^9 /L)	5/34	14.7
High ALT/AST (> 2 normal ranges)	19/34	55,9
High ALP (> 2 normal ranges)	23/34	67.6
High GGT (> 5 normal ranges)	25/34	73.5
High total bilirubin (> 21 μmol/L)	11/34	32.4
High total cholesterol (>5.3 mmol/L)	16/32	50
Low albumin (< 35 g/L)	6/34	17.6
Low prothrombin index (< 60%)	3/34	8.8

Table 2. Clinical characteristics of liver damage in ACA-positive pSS patients

	Number of patients	
Sign	**№**	**%**
Right upper quadrant pain	7/34	20.6
Jaundice	3/34	8.8
Itchy skin	5/34	14.7
Hepatomegaly	13/34	38.2
Splenomegaly	6/34	17.6
Hepatic encephalopathy	2/34	5.9
Ascites	1/34	2.9
Esophageal varices	3/34	8.8
Portal hypertension	5/34	14.7
Osteoporosis	8/12	66.6
Cirrhosis (Child-Pugh):	5/34	14.7
A	2/5	40
B	2/5	40
C	1/5	20

(Table 1). More than a half of the patients had an increase in serum IgM levels. There were isolated cases of hypergammaglobulinemia caused by an increase in IgM level, while IgG levels remained within the normal range, with the exception of 2 patients who were subsequently diagnosed with PBC/AIH overlap syndrome, as well as cytopenia associated with hypersplenism in progressive liver cirrhosis. A small number of patients had impaired liver synthetic function, which was associated with severe liver damage in cirrhosis.

Liver damage in the majority of ACA-positive pSS patients was asymptomatic (Table 2). With dynamic follow-up, the median of which was 3 years (min. 1 year, max. 18 years), no progression of liver failure was noted. Signs of cirrhosis were detected in 5 (14.7%) patients. On the basis of clinical, laboratory and morphological data, AMA-positive PBC was diagnosed in 18 patients, of whom 4 had an overlap syndrome with AIH, which in 3 cases was established based on the results of liver biopsy, in 1 – according to the clinical and laboratory data. Morphological examination of liver biopsies revealed AMA-negative PBC in 3 patients, isolated AIH - in 1 patient. Also, 2 of 9 asymptomatic AMA-positive patients who underwent liver biopsy had signs of PBC.

Cholestasis of unspecified genesis was established in 5 AMA-negative patients after exclusion of cholelithiasis, drug or viral hepatitis, and steatohepatitis. Since these patients did not undergo liver biopsies, AMA-negative PBC cannot be ruled out.

Thus, liver biopsy performed in 13 patients made it possible to diagnose PBC in 12 cases, including 3 cases of overlap syndrome with AIH and 1 case of isolated AIH.

In the remaining 9 cases, the diagnosis of PBC (in 1 case in combination with AIH) was established only on the basis of clinical and laboratory data. Histological examination revealed signs of stage I PBC in 7 patients, stage II in 1, and stage III in 4 patients.

During the period of dynamic follow-up (median 7 years; min. 2 years, max. 15 years), 7 patients with stage I PBC (repeated biopsy was not performed) and 7 patients with asymptomatic AMA-positivity had no signs of progression of liver damage according to the survey data. In this regard, we believe that these patients do not have true PBC, but epitheliitis of the biliary ducts, which is a manifestation of glandular lesions in pSS.

Discussion. The high prevalence of PBC in pSS and vice versa may indicate that these conditions may have common etiopathogenetic mechanisms. Both diseases occur mainly in women of perimenopausal age [5]. The pathogenetic substrate of both pSS and PBC is a chronic destructive immune-mediated epitheliitis that develops in the salivary/lacrimal glands or bile ducts [40]. PBC and pSS are associated with hyperactivity of B-cell immunity, manifested in the production of highly specific autoantibodies (anti-Ro/La and AMA), increased serum levels of BAFF (B-cell Activating Factor belonging to the TNF Family) and IgM [40, 41] and frequent combination with a limited form of SSc and ACA [10, 11, 34], which was confirmed in our study, in which a third of patients had signs of SSc. The histological and immunohistochemical features of salivary gland and liver lesions in these diseases are largely similar and are characterized by lymphoid infiltration of the ductal epithelium with a predominance of CD4-positive T-lymphocytes and B-lymphocytes [41]. Some researchers, substantiating their assumptions with a large number of common features of pSS and PBC, believe that both diseases are different manifestations of the same autoimmune process. [42, 43], and consider it appropriate to routinely determine ACA in PBC, and AMA in pSS and SSc [44].

To establish the diagnosis of PBC, it is sufficient to detect 2 of 3 criteria: 1) persistent (> 6 months) biochemical signs of cholestasis (ALP> 2 normal values or GGTP> 5 normal values); 2) detection of diagnostic AMA titers; 3) detection of chronic

non-suppurative destructive cholangitis of medium and small ducts with liver biopsy [17, 38, 45, 46]. Thus, liver biopsy is necessary only if cholestasis is detected in AMA-negative patients, while it is optional in AMA-positive patients, but it allows to assess the stage and activity of the inflammatory process, as well as to establish the overlap syndrome with AIH [17, 38, 47]. Some researchers suggest that AMAs are the most specific autoantibodies in clinical immunology [5]. However, in pSS, AMAs are present in 22–27% of cases, and not always in patients with impaired liver function [18, 48, 49]. At the same time, it was revealed that, with long-term follow-up, AMA-positivity predicts progression to PBC with a high degree of probability [50–53], which is confirmed by our study: in 2 patients with asymptomatic AMA-positivity, liver biopsy revealed histological stage I of PBC.

The morphological substrate of PBC is destructive non-suppurative cholangitis, histological changes are conditionally subdivided into 4 stages, depending on the severity and volume of pathological changes [17, 38, 40, 54]. H.M. Moutsopoulos et al. [42], when observing 300 pSS patients, in 7% of cases found signs of liver damage, proceeding subclinically or asymptomatically with an increase in liver enzymes; almost all patients were AMA-positive. Liver biopsy in 92% of AMA-positive patients showed signs of chronic destructive granulomatous cholangitis with damage to small and medium biliary ducts without signs of bridging necrosis, identical to the histological changes characteristic of stage I PBC. Based on the data obtained, the authors concluded that liver damage in pSS is rare, subclinical in nature, does not lead to the formation of cirrhosis, is associated with AMA and histologically corresponds to PBC stage I, which is confirmed by the results of our study. Based on the absence of liver cirrhosis in the examined patients, H.M. Moutsopoulos et al. [42] suggested using the term «autoimmune cholangitis» to denote a mild lesion of the biliary ducts in pSS and including it in the glandular manifestations of the disease. Thus, stage I PBC is a nonspecific morphological sign, since similar changes can characterize the lesion of the biliary ducts in pSS. It should be noted that at present in hepatology the term «autoimmune cholangitis» has a clear definition and denotes clinical, laboratory and morphological signs of PBC in AMA-negative, but ANA-positive patients [55]. At the same time, most hepatologists consider it unreasonable to isolate autoimmune cholangitis as an independent nosological unit, regarding it as AMA-negative form of PBC [56–60]. Therefore, in our study, we designated clinical cases of non-progressive cholestatic liver damage without signs of cirrhosis, accompanied by histological changes characteristic of stage I PBC, as «pSS-associated epitheliitis of the biliary ducts». Since the natural course of PBC is extremely variable – from the absence of disease progression over several decades to the rapid development of liver failure over several years [46], a long-term follow-up of such patients is required to distinguish between pSS-associated epitheliitis of the biliary ducts and slowly progressive form of «classic» PBC. Our data are similar to the results of the study by G.S. Hatzis et al. [31], in which PBC was detected in 6.6% of patients with pSS, while most of them had stage I, and had a mild, slowly progressive course of the disease; none of the patients showed signs of cirrhosis over 5.5 years of follow-up. Earlier, when analyzing the histological stages of liver damage in 48 pSS patients having signs of liver dysfunction and highly positive for anti-Ro/La, ACA and AMA, we found stage I PBC in 34% of cases [61]. Only an older age of patients, the presence of morphological changes corresponding to > stage 2 PBC, overlap syndrome with AIH, and high levels of alkaline phosphatase distinguished the combination of pSS with PBC, AIH or sclerosing cholangitis from pSS-associated epitheliitis of the biliary ducts. The absence or minimal impairment of the liver function, histological stage I of PBC, the absence of progression of liver damage during the long-term follow-up of patients receiving anti-B-cell therapy, made it possible to draw a conclusion about the presence of pSS-associated liver damage [61]. Portal hypertension, which is often found in PBC patients and is known to precede other signs of cirrhosis [64], was detected in the present study only in 14.7% of cases, which is inconsistent with the results obtained by M. Nakamura et al. [19], L. Gao et al. [20].

Thus, according to the study, in ACA-positive pSS patients, autoimmune liver damage was detected in 28.6% of cases and manifested as pSS-associated epitheliitis of the biliary ducts or PBC. Considering the literature data and the results of our studies, indicating a high incidence of pSS, PBC and SSc in ACA-positive patients, we recommend examining this group of patients in order to exclude these diseases. The combination of PBC and ACA-positive pSS is often associated with increased AMA and IgM levels, high ALP levels and, in most cases, is characterized by a slowly progressive asymptomatic course, rarely leading to liver cirrhosis. AMA-positivity in the absence or minimal functional impairment of the liver with histological signs of stage I PBC corresponds to pSS-associated epitheliitis of the biliary ducts; patients with pSS and PBC have more severe functional liver impairment and advanced stages of liver damage according to biopsy data; with long-term follow-up, 14.7% of them may develop various stages of liver cirrhosis.

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