Prevalence and Longterm Course of Primary Biliary Cirrhosis in Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To study the prevalence of primary biliary cirrhosis (PBC) and its progression in patients with primary Sjögren's syndrome (SS).

Methods. We investigated 410 patients with primary SS, without history of liver disease, for the presence of PBC based on a retrospective review of clinical, biochemical, immunologic, and histologic data.

Results. Thirty-six (8.8%) patients had cholestatic liver biochemistry. Of them, 21 (5.1%) had positive antimitochondrial autoantibodies (AMA) detected by indirect immunofluorescence, while 15 were AMA-negative. Ten of the 21 AMA-positive patients and 7 of the 15 AMA-negative patients were further investigated with liver biopsy, the result of which was compatible with PBC in all but one (AMA-negative) patient. Overall, 27 (6.6%) patients had definite (n = 10), probable (n = 11), or AMA-negative (n = 6) PBC. Pathologically, most PBC lesions were stage 1. Five patients had a second liver biopsy, with no significant histological deterioration.

Conclusion. PBC is a rather uncommon development in patients with primary SS. The disease appears to be pathologically mild, with a propensity for slow progression, as assessed clinically, biochemically, and histologically. (First Release Aug 15 2008; J Rheumatol 2008;35:2012–6)

Key Indexing Terms:
SJÖGREN'S SYNDROME
ANTIMITOCHONDRIAL AUTOANTIBODIES
PRIMARY BILIARY CIRRHOSIS
CHRONIC LIVER DISEASE

Primary biliary cirrhosis (PBC) is a chronic, progressive autoimmune liver disease of unknown etiology characterized by inflammatory destruction of septal and interlobular bile ducts that leads to cholestatic chronic liver disease and, eventually, to cirrhosis. PBC is associated with other autoimmune diseases such as Sjögren's syndrome (SS)[1], autoimmune thyroiditis[2], rheumatoid arthritis[3], ankylosing spondylitis[4], polymyositis[5], scleroderma[6], and thrombocytopenia[7]. Patients with a cholestatic biochemical pattern, positive antimitochondrial autoantibody (AMA) test, and hepatic histological features compatible with PBC would generally be diagnosed as having PBC[8], irrespective of the clinical picture[9].

SS is a chronic, systemic autoimmune disorder characterized as autoimmune epithelitis[10]. It primarily affects the lacrimal and salivary glands and is the result of lymphocyte-mediated destruction of exocrine glands, leading to diminished or absent glandular secretions and mucosal dryness[11], and commonly presenting with dry eyes and mouth along with the sicca manifestations of other exocrine glands[12].

SS occurs alone, as primary SS, or in association with various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, as secondary SS[13-15].

PBC has been shown to be associated with primary SS[16]. Indeed, in several studies the most common autoimmune disorder associated with PBC is SS, with a reported prevalence of SS in PBC patients ranging from 69% to 81%[16-18].

Conversely, abnormal liver biochemistry, while not characteristic of the disease, is often present in patients with primary SS, with PBC being the leading underlying pathology[19].

We studied the prevalence of PBC in a large cohort of patients with primary SS, sought to define the natural history of the disease, and followed the progression of hepatic pathology in the affected patients. We reviewed the files of 410 patients with primary SS to identify those with liver involvement based on clinical, biochemical, immunological, and histological data. Results of longterm followup required to meet the objectives of our study are reported.

MATERIALS AND METHODS

Patients. Four hundred ten patients (379 women and 31 men, median age 61 yrs, range 27–84) with a diagnosis of primary SS were included in the study (Figure 1). All patients met 4 or more preliminary diagnostic criteria for SS as proposed by the European Community Study Group[20]. Notably, all patients fulfilled both immunological criteria and positive salivary gland biopsy. No patient exhibited stigmata of autoimmune hepatitis, had a history of hepato-

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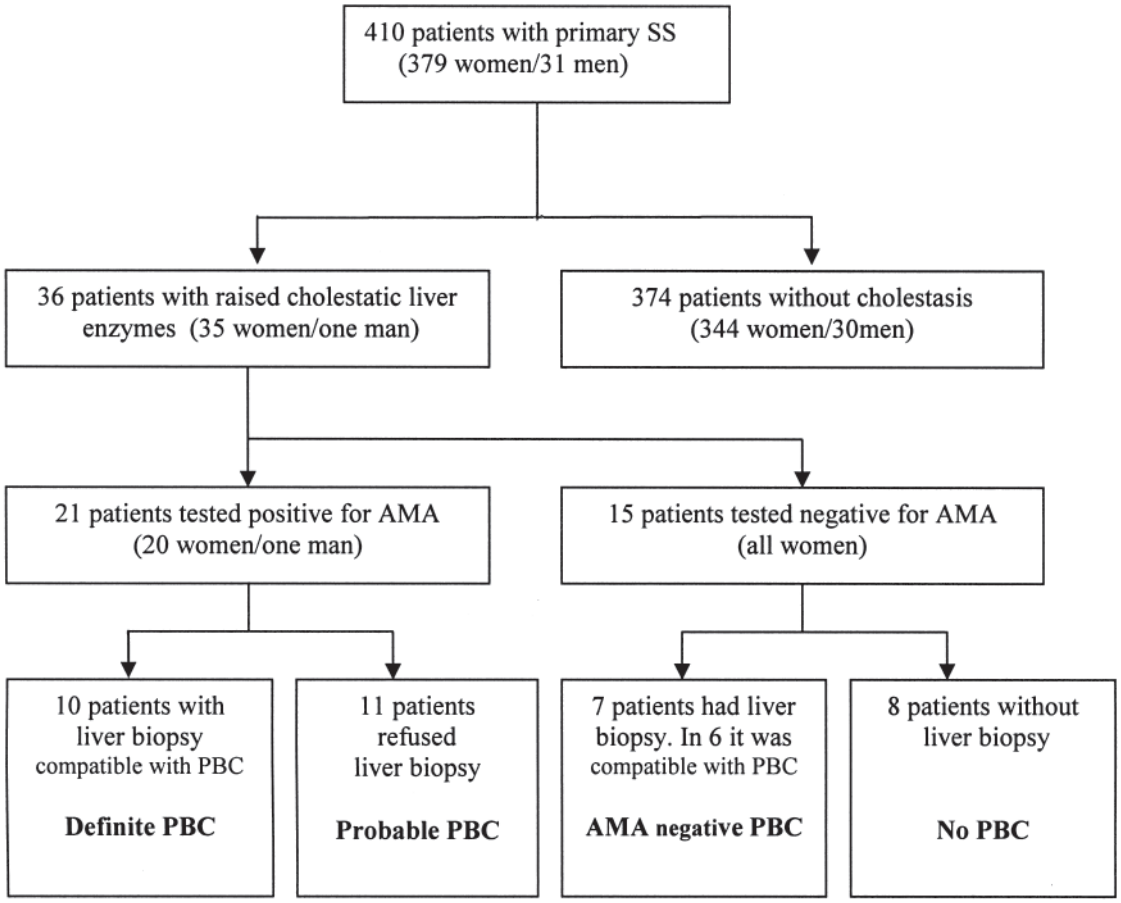

Figure 1. Prevalence of primary biliary cirrhosis (PBC) in patients with primary Sjögren's syndrome (SS). AMA: antimitochondrial autoantibody.

toxic drug use or alcohol abuse, or had signs of metabolic or lymphoproliferative diseases. Cases of SS associated with hepatitis B or C virus or HIV infection were excluded. All patients with SS were followed up at the Rheumatologic Clinic, Department of Pathophysiology, Athens University School of Medicine, where they undergo routine clinical, biochemical, and immunological reevaluation at least every 6 months.

Study protocol. Patients' files were reviewed for presence of biochemical cholestasis in the form of a raised alkaline phosphatase (ALP), its hepatic origin confirmed by an elevated gamma-glutamyltransferase (γ-GT). Serum levels of ALP, γ-GT, bilirubin, alanine aminotransferase (ALT), and prothrombin time/INR were recorded. Of those with a cholestatic profile (almost always present on multiple biochemical measurements), we ascertained the outcome of AMA tests, or if one was not available, it was ordered. All AMA tests were done by the indirect immunofluorescence method, using rat stomach and kidney. Titers of ≥ 40 were considered positive.

Diagnosis and chronology of PBC development. The first time there was a record of biochemical cholestasis, supported by subsequent evidence favoring PBC, it was deemed to represent the onset of PBC. The diagnosis and management of PBC followed the American Association for the Study of Liver Diseases practice guidelines[21].

Histological data. Seventeen patients with primary SS and cholestatic enzyme pattern had diagnostic liver biopsies, of which 5 had followup biopsies to assess the course of disease. Histological scoring was based on Scheuer's staging classification[22]. Cardinal histological features of stages 1–4 include destruction of septal and larger interlobular ducts, bile ductular proliferation, scarring with septal fibrosis, and nodular cirrhosis, respectively.

Therapy. Patients with primary SS who developed PBC were treated with ursodeoxycholic acid (Ursodiol, 13–15 mg/kg daily).

RESULTS

Among the 410 patients with primary SS, 36 (8.8%) had liver involvement evidenced by raised serum ALP and/or γ-GT activity, of which 21 (5.1%) were AMA-positive and 15 AMA-negative. Of the 21 positive patients, 10 had liver biopsy findings compatible with PBC (stage 1: 6 cases; stage 1–2: 1 case; stage 2: 1 case; stage 3: 2 cases), and we considered this group to have definite PBC. The other 11 patients refused liver biopsy and we considered them to have probable PBC (Figure 1).

Of the 15 patients with a cholestatic enzyme pattern but negative AMA, 7 consented to have a liver biopsy. Findings were compatible with stage 1 PBC in 6 patients, and nonspecific in one. We considered those 6 patients to have AMA-negative PBC. The patient with a negative biopsy and the remaining 8 patients with cholestasis, negative AMA, and no liver biopsy were deemed to have cholestasis of unknown etiology. Three of those 8 patients had increased ALT activity (> 1.5 × the upper limit of normal) as well as elevated cholestatic enzymes. There was only one other patient with a raised ALT, a case of AMA-negative PBC.

Overall, 27 (6.6%) patients with primary SS were found to have definite (n = 10), probable (n = 11), or AMA-negative PBC (n = 6). All but one were women. During a mean followup of 66 months after diagnosis of PBC, none developed clinical, laboratory, or imaging evidence of liver cirrhosis.

The mean followup of SS patients with PBC was 93 months (SD ± 51.25) compared to 60.4 months (SD ± 46.39) for SS patients without cholestasis.

The mean interval between diagnosis of SS and the manifestation and diagnosis of PBC in the affected patients was 28 months (range 3–120).

On followup of patients with PBC, most remained stable. One patient deteriorated clinically, with worsening fatigue, intensified pruritus, and increasing hepatomegaly, while 8 patients exhibited heightened cholestasis, with markedly elevated ALP and γ-GT (Table 1).

Of the 6 patients with AMA-negative PBC none developed positive AMA during a mean followup of 47 months. Similarly, of the 9 patients with cholestasis of unknown etiology, all remained AMA-negative during a mean followup of 28 months (range 3–79).

A comparison of the histological features of 5 paired liver biopsies, from 4 patients with definite PBC and one patient with AMA-negative PBC, taken at a mean interval of 46 months apart (range 24–84) showed no significant change.

DISCUSSION

A certain degree of overlap between primary SS and PBC has already been reported[1,23]. However, there is a dearth of data on the clinical course of PBC in patients with overlap disease. In addition, reported prevalence rates of PBC in primary SS were largely based on smaller cohorts.

In our study, patients with cholestatic liver biochemistry and positive AMA were diagnosed as having definite PBC if they had a liver biopsy compatible with PBC (n = 10), or probable PBC if they lacked a liver biopsy (n = 11). Another 6 patients with a biopsy-proven PBC had negative AMA and were diagnosed as having AMA-negative PBC. This figure (6 of 27 patients, 22%) is higher than the commonly reported prevalence of AMA-negative PBC of around 5%–10%, although similarly high numbers have been reported recently in PBC not associated with other diseases[24]. Because of this, and the relatively small number of index cases in our study, it would be problematic to claim that SS-associated PBC cases are more often AMA-negative.

Under the definitions above, 6.6% of our patients with primary SS had definite, probable, or AMA-negative PBC. This figure is in agreement with a 3%–9% prevalence of PBC reported in patients with primary SS[23,25-27]. Lindgren, *et al* found abnormal serum liver biochemistry in up to 27% of patients with primary SS, with two-thirds of them having cholestasis, while PBC was diagnosed in 9%[25]. In a study of 300 patients with primary SS, Skopouli, *et al* found that 7% had some evidence of liver disease and 6.6% had positive AMA[23]. The study of Ramos-Casals, *et al* with 475 SS patients was significant in that liver involvement was detected in 27%, but most cases were accounted for by chronic HCV disease (13%), with PBC at 3.3%[27]. This variation in the prevalence of PBC among studies is not readily explainable since essentially the same diagnostic criteria were used for SS. Nevertheless, the strength of the association between SS and PBC looms large when considering the prevalence of PBC in the general population at around 0.01%–0.03%. However, since SS is an uncommon disease, the absolute number of SS-associated PBC cases is distinctly small.

Positive AMA is an acknowledged serological hallmark of

Table 1. Progression of primary biliary cirrhosis (PBC) or cholestasis in patients with primary Sjögren's syndrome.

Patients	Definite PBC, n = 10	Probable PBC, n = 11	AMA-negative PBC, n = 6	Cholestasis of Unknown Etiology, n = 9
Followup, mo, mean (range)	77.4 (9–180)	64.9 (2–120)	46.6 (7–106)	28 (3–79)
Clinical progression				
Stable	10	10	6	9
Deterioration	0	1	0	0
Biochemical progression				
Stable	7	7	5	9
Deterioration	3	4	1	0
Histologic progression†	4	—	1	—
Stable	4	—	1	—
Deterioration	0	—	0	—
ALP*, U/l, mean (range)	185.6 (55–439)	257.1 (116–851)	199.3 (62–442)	192.9 (64–732)
γ-GT*, U/l, mean (range)	56.1 (9–95)	46.7 (13–153)	91.2 (13–159)	43.12 (11–217)
ALT*, U/l, mean (range)	23.6 (13–35)	34.5 (15–39)	28 (13–50)	34.25 (12–57)
Bilirubin*, mg/dl, mean (range)	0.77 (0.23–1.15)	0.72 (0.38–0.98)	0.9 (0.51–1.9)	0.81 (0.6–1.25)
INR*, mean (range)	1.07 (0.99–1.2)	1.04 (1–1.09)	1.06 (1.01–1.18)	1.09 (1.02–1.19)

AMA: antimitochondrial autoantibody; ALP: alkaline phosphatase (normal 41–280 U/I); γ-GT: gamma-glutamyltransferase (normal range 6–50 U/l); ALT: alanine aminotransferase (normal 5–40 U/l); bilirubin (normal 0.3–1.2 mg/dl); INR: international normalized ratio (normal 1.0). † 5 patients with paired biopsies; * at end of followup.

PBC[9,28]. Of the available methods for its detection, indirect immunofluorescence is less sensitive than, but equally as specific as ELISA or Western blot analysis. In series of patients with primary SS, where AMA was evaluated by the former method, positive results range from 1.6% to 13%[23,25,26]. On the other hand, the use of ELISA or Western blot increased AMA positivity to 22%–27%[23,29,30]. Positive results by the latter methods are virtually diagnostic of PBC, or at least suggest that the patient is at substantial risk of developing PBC over the next 5 to 10 years[31]. This issue was illustrated in the study of Skopouli, *et al*, where no patient testing positive for antibodies to pyruvate dehydrogenase E_2 complex by ELISA, but negative by immunofluorescence, had elevated liver enzymes[23]. By choosing the latter, less sensitive method we were more likely to circumvent the possibility of a 5–10 year gap between time of detection of AMA and manifestation of the disease and to identify patients with established clinical, biochemical, and histological features that would allow us to follow their course over time. In addition, this would preclude possible lead-time bias in the evaluation of treatment regimens.

On the other hand, it should be acknowledged that this approach might have underestimated the prevalence of PBC since 8 AMA-negative patients with cholestasis of unknown etiology did not have liver biopsy, which might have converted some of them to AMA-negative PBC cases. Another criticism of our study might be that had the entire cohort been tested for AMA, we might have unearthed AMA-positive cases associated with normal cholestatic enzymes. Although this combination has been reported[27], it is not sufficiently common to have made a material difference to our results. Characteristically, of 7829 autoantibody screen tests done at a regional immunology laboratory on patients with suspected autoimmune disorders but no suspicion of liver disease, there were only 31 (0.4%) cases with positive AMA[32]. In addition, half the patients with normal ALP had raised γ-GT levels that, according to our protocol, would have qualified them for entry into our study.

The initiating events leading to autoimmunity against epithelial cells lining the intrahepatic bile ducts and salivary ducts are largely unknown, but it should be noted that primary SS and PBC share many common features. In both, the inflammation starts around the ducts and both epithelial populations inappropriately express class II HLA molecules. In addition, CD4-positive T cells predominate in the hepatic lesions of severe biliary cirrhosis, as they do in the salivary gland lesions of primary SS[33].

Thus, it appears that common pathogenetic mechanisms operate in the 2 diseases, although their autoantibodies are different. Indeed, increasing evidence suggests that PBC and primary SS are different expressions of the same autoimmune-mediated epithelitis[10,34]. On the other hand, a viral link has also been suggested, with coxsackievirus and retrovirus being implicated in the induction and maintenance of primary SS and PBC, respectively[35,36].

It is an important question whether the retrospective design of our study might have influenced its results. Of the patients initially identified with biochemical cholestasis, none were lost to followup; thus it is unlikely that advanced cases of PBC were missed. In addition, most of the patients presented in our outpatient department, rather than being referred from tertiary centers, hence the cases of PBC were culled from a SS cohort with a wide spectrum of symptoms and disease severity, decreasing the possibility of exaggerated representation of PBC cases. On the other hand, the regular followup of SS patients in our clinic might have contributed to earlier diagnosis — and stage — of PBC, but this possibility is countered by our study's long followup period, which allowed a more convincing picture to emerge of the natural history of the disease.

The clinical, biochemical, and immunological followup over a mean period of 66 months after diagnosis of PBC showed the disease to be stable in most patients. One patient with probable PBC showed clinical deterioration, while 8 patients (3 with definite PBC, 4 with probable PBC, and one with AMA-negative PBC) showed biochemical deterioration.

Liver histology in 5 patients with a second liver biopsy showed no change in the pathological stage of PBC, after a mean interval of 46 months. Although sampling errors could account for the lack of histological progression of the disease, the pathologic picture was mirrored in and supported by the clinical and biochemical findings on long followup. Nevertheless, because of the modest number of baseline liver biopsies and the small number of second biopsies we may have underestimated the severity of the disease, particularly since florid lesions have been reported even in asymptomatic patients.

Given the large cohort of patients and the long followup, our study provides fairly robust answers regarding prevalence of PBC in primary SS, its clinical expression, histopathologic features, and, indeed, the natural history and evolution of SS-associated PBC.

Our study showed that about 7% of patients with primary SS have definite, probable, or AMA-negative PBC. Most hepatic lesions are at an early pathologic stage. More importantly, the disease appears to show a propensity for slow progression, as evidenced by clinical, biochemical, and histologic data.

REFERENCES

1. Tsianos EV, Hoofnagle JH, Fox PC, et al. Sjögren's syndrome in patients with primary biliary cirrhosis. Hepatology 1990;11:730-4.
2. Crowe JP, Christensen E, Butler J, et al. Primary biliary cirrhosis: the prevalence of hypothyroidism and its relationship to thyroid autoantibodies and sicca syndrome. Gastroenterology 1980;78:1441-53.
3. Marx WJ, O'Connell DJ. Arthritis of primary biliary cirrhosis. Arch Intern Med 1979;139:213-6.
4. Vargas CA, Medina R, Rubio CE, Torres EA. Primary biliary cirrhosis associated with ankylosing spondylitis. J Clin Gastroenterol 1994;18:263-4.
5. Boki KA, Dourakis SP. Polymyositis associated with primary biliary cirrhosis. Clin Rheumatol 1995;14:375-8.

6. Miller F, Lane B, Soterakis J, D'Angelo WA. Primary biliary cirrhosis and scleroderma. Arch Pathol Lab Med 1979;103:505-9.
7. Feistauer SM, Penner E, Mayr WR, Panzer S. Target platelet antigens of autoantibodies in patients with primary biliary cirrhosis. Hepatology 1997;25:1343-5.
8. Jeffrey GP, Reed WD, Shilkin KB. Primary biliary cirrhosis: clinicopathological characteristics and outcome. J Gastroenterol Hepatol 1990;5:639-45.
9. Metcalf JV, James OFW, Palmer JM, Jones DE, Bassendine MF. Natural history of early primary biliary cirrhosis. Lancet 1996;348:1399-402.
10. Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. Clin Immunol Immunopathol 1994;72:162-5.
11. Moutsopoulos HM, Chused TM, Mann DL, et al. Sjögren's syndrome (sicca syndrome) current issues. Ann Intern Med 1980;92:212-6.
12. Fox RI. Epidemiology, pathogenesis, animal models, and treatment of Sjögren's syndrome. Curr Opin Rheumatol 1994;6:501-8.
13. Andonopoulos AP, Drosos AA, Skopouli FN, Acritidis NC, Moutsopoulos HH. Secondary Sjögren's syndrome in rheumatoid arthritis. J Rheumatol 1987;14:1098-103.
14. Moutsopoulos HM, Klippel JH, Pavlidis N, et al. Correlative histologic and serologic finding of sicca syndrome in patients with systemic lupus erythematosus. Arthritis Rheum 1980;23:36-40.
15. Drosos AA, Andonopoulos AP, Costopoulos JS, Stavropoulos ED, Papadimitriou CS, Moutsopoulos HM. Sjögren's syndrome in progressive systemic sclerosis. J Rheumatol 1988;15:965-8.
16. Alarcon-Segovia D, Diaz-Jouanen E, Fishbein E. Features of Sjögren's syndrome in primary biliary cirrhosis. Ann Intern Med 1973;79:31-6.
17. Golding PL, Brown R, Mason AMS, Taylor E. Sicca complex in liver disease. Br Med J 1970;4:340-2.
18. Crowe JP, Christensen E, Bulter J, et al. Primary biliary cirrhosis: the prevalence of hyperthyroidism and its relationship to thyroid autoantibodies and sicca syndrome. Gastroenterology 1980;78:1437-41.
19. Kojima H, Uemura M, Sakurai S, et al. Clinical features of liver disturbance in rheumatoid diseases: clinicopathological study with special reference to the cause of liver disturbance. J Gastroenterol 2002;37:617-25.
20. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Arthritis Rheum 1993;36:340-7.
21. Heathcote EJ. Management of primary biliary cirrhosis. Hepatology 2000;31:1005-13.
22. Scheuer P. Primary biliary cirrhosis. Proc R Soc Med 1967;60:1257-60.
23. Skopouli FN, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjögren's syndrome. Br J Rheumatol 1994;33:745-8.
24. Lindor KD. Primary biliary cirrhosis. In: Boyer TD, Wright TL, Manns MP, editors. Zakim and Boyer's hepatology. 5th ed. Amsterdam: Saunders Elsevier; 2006:806.
25. Lindgren S, Manthorpe R, Eriksson S. Autoimmune liver disease in patients with primary Sjögren's syndrome. J Hepatol 1994; 20:354-8.
26. Csepregi A, Szodoray P, Zeher M. Do autoantibodies predict autoimmune liver disease in primary Sjögren's syndrome? Data of 180 patients upon a 5 year follow-up. Scand J Immunol 2002;56:623-9.
27. Ramos-Casals M, Sanchez-Tapias J-M, Pares A, et al. Characterization and differentiation of autoimmune versus viral liver involvement in patients with Sjogren's syndrome. J Rheumatol 2006;33:1593-9.
28. Hasselstrom K, Nilsson LA, Wallerstedt S. The predictive value of antimitochondrial antibodies in establishing the diagnosis of primary biliary cirrhosis. Scand J Gastroenterol 1988;23:103-6.
29. Zurgil N, Bakimer R, Moutsopoulos HM, et al. Antimitochondrial (pyruvate dehydrogenase) autoantibodies in autoimmune rheumatic diseases. J Clin Immunol 1992;12:201-9.
30. Fujikura S, Davis PA, Prindiville T, Leung P, Fox RI, Gershwin ME. Sjögren's syndrome and primary biliary cirrhosis: presence of autoantibodies to purified mitochondrial 2-oxoacid dehydrogenases. J Rheumatol 1990;17:1453-7.
31. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med 2005;353:1261-73.
32. Mitchison HC, Bassendine MF, Hendrick A, et al. Positive antimitochondrial antibody but normal alkaline phosphatase: is this primary biliary cirrhosis? Hepatology 1986;6:1279-84.
33. Abraham S, Begun S, Isenberg D. Hepatic manifestations of autoimmune rheumatic diseases. Ann Rheum Dis 2004;63:123-9.
34. Tsuneyama K, van de Water J, Yamazaki K, et al. Primary biliary cirrhosis and epithelitis: evidence of abnormal salivary gland immunohistochemistry. Autoimmunity 1997;26:23-31.
35. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjögren's syndrome. Arthritis Rheum 2004;50:2897-902.
36. Mason AL, Xu L, Guo L, et al. Detection of retroviral antibodies in primary biliary cirrhosis and other idiopathic biliary disorders. Lancet 1998;351:1620-4.