Primary Biliary Cirrhosis in Antimitochondrial Antibody-Negative Patients: Chang Gung Memorial Hospital Experience

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Background: It is known that some patients with clinical, histological, and laboratory features of primary biliary cirrhosis (PBC) lack serum antimitochondrial antibodies (AMAs). In Asian countries, clinical information regarding AMA-negative PBC is still limited. In this report, we reviewed our patients with AMA-negative PBC in order to further understand this disease.

Methods: Clinical features of 36 patients with PBC diagnosed by the histopathologic characteristics of the liver at Chung Gung Memorial Hospital--Lin Kou Medical Center from 1985 to 2000 were reviewed. Of them, 15 were negative and 21 were positive for serum AMAs at presentation. Clinical, biochemical, immunological, and histological parameters were compared between these 2 groups.

Results: There were only a few differences between the AMA-negative and -positive groups. Significantly more asymptomatic patients ($p = 0.0017$) and a higher positive rate of serum antinuclear antibodies (ANA) ($p = 0.0323$) were observed in the AMA-negative group. Otherwise, there were no significant differences with regard to clinical, biochemical, immunological, or histological parameters. Interestingly, 4 of the 15 patients with AMA-negative PBC became AMA positive during 10, 23, 47, and 56 (mean, 34) months of follow-up.

Conclusions: The results show that patients with AMA-negative PBC tend to be asymptomatic and ANA positive. Some patients may develop positive AMA during follow-up. Our data imply that AMA-negative PBC might be a variant of AMA-positive PBC, rather than a separate disease.

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Key words: **primary biliary cirrhosis, antimitochondrial antibody, antinuclear antibody.**

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic liver disease of unknown etiology. It is characterized by progressive destruction of small intrahepatic bile ducts with portal inflammation leading to hepatic fibrosis and cirrhosis.[1] The most important diagnostic marker for PBC is antimitochondrial antibodies (AMAs).[2] However, AMAs are not detected by indirect immunofluorescence technique in 5% to 32% of patients whose clinical, histological, and laboratory features are diagnostic of PBC.[3-8] In order to distinguish them from AMA-positive patients, the term autoimmune

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cholangitis (AIC) has been used to describe PBC patients without serum AMAs.[9] Whether AMA-negative PBC is a variant of AMA-positive PBC[4,8,10] or a separate disease entity[11-13] remains inconclusive.

In Asian countries, information regarding AMA-negative PBC is still limited.[6] Furthermore, seroconversion from negative to positive for AMAs, or vice versa, has been observed clinically in some patients during the course of the disease.[8,14] In this study, we reviewed our patients with AMA-negative PBC in order to further understand this disease.

METHODS

Data on 36 PBC patients who were diagnosed as having PBC based on the histopathologic features of the liver at the Chung Gung Memorial Hospital--Lin Kou Medical Center from 1985 to 2000 were collected. The clinical, biochemical, and serological data at the time of presentation were analyzed. Clinical parameters included patient gender, age at presentation, symptoms, and associated autoimmune disorders. Biochemical parameters included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), and total bilirubin. Immunological parameters included immunoglobulin-M (IgM), γ-globulin, and anti-nuclear (ANAs) and anti-smooth muscle antibodies (ASMAs). Histological parameters included histological grading and specific histological findings. Twenty-one patients who tested positive for serum AMAs at presentation were referred to as the AMA-positive group. The other 15 patients who tested negative for serum AMAs were referred to as the AMA-negative group.

Serum ANAs, AMAs, and ASMAs were determined by indirect immunofluorescent tests. An ANA titer $\geq$ 1:160, an AMA titer $\geq$ 1:20, and an ASMA titer $\geq$ 1:20 were interpreted as positive in this study. Histological staging was performed according to criteria published by Ludwing et al.[15]

Data in the text and tables are expressed as the mean $\pm$ standard deviation. Differences were compared by 2-sample *t*-test for continuous data and Fisher's exact test for discontinuous data. Results with a p value < 0.05 were considered statistically significant.

RESULTS

Of these 36 patients, 31 (86.1%) were female and 5 (13.9%) were male. The mean age of presentation was 51.8 $\pm$ 11.5 (range, 29 to 75) years. At presentation, 21 patients (58.3%) were positive and 15 (41.7%) were negative for serum AMAs. The clinical features in patients positive for serum AMAs and those negative for serum AMAs are listed in Table 1. Fatigue, pruritus, and jaundice were the most common initial symptoms. Eleven patients (30.6%) including 9 in the AMA-negative group and 2 in the AMA-positive group (9/15 vs. 2/21, $p = 0.0017$) had no symptoms at the time of presentation. Associated autoimmune disorders were observed in 6 patients: 1 patient with systemic sclerosis, 1 patient with systemic lupus erythematosus, 3 patients with autoimmune thyroiditis, and 1 patient with immune thrombocytopenic purpura. There were no significant differences between AMA-negative and -positive patients with respect to patient gender, age, initial symptoms, or associated autoimmune disorders.

Table 2 shows a comparison of liver biochemistries between AMA-negative and -positive patients. No significant differences were found in serum levels of AST, ALT, ALP, γ-GT, or total biliru-

Table 1. Clinical Parameters in AMA-Negative and -Positive Patients

Parameter	AMA-negative patients (N = 15)	AMA-positive patients (N = 21)	*p**
Female: male ratio	13 : 2	18 : 3	0.3704
Age at diagnosis (yr) (mean ± SD)	48.1 ± 9.2	54.3 ± 12.5	0.0954
Asymptomatic patients	9	2	0.0017
Associated symptoms			
Pruritus	5	11	0.1449
Fatigue	1	6	0.0975
Jaundice	2	5	0.2560
Associated disorders			
Systemic sclerosis	0	1	0.5833
SLE	1	0	0.4167
Autoimmune thyroiditis	0	3	0.1863
ITP	1	0	0.4167

*A p-value > 0.05 indicates no statistical significance; SD, standard deviation; AMA, anti-mitochondrial antibody; SLE, systemic lupus erythematosus; ITP, immune thrombocytopenic purpura.

Table 2. Biochemical Parameters in AMA-Negative and -Positive Patients

Parameter at time of diagnosis (normal range)	AMA-negative patients (mean ± SD) (N = 15)	AMA-positive patients (mean ± SD) (N = 21)	*p**
Total bilirubin (< 1.3 mg/dl)	2.7 ± 3.5	2.3 ± 2.2	0.6983
AST (0-34 U/L)	128.3 ± 112.8	108.7 ± 55.5	0.5403
ALT (0-36 U/L)	140.2 ± 116.4	113.5 ± 46.0	0.4131
ALP (28-94 U/L)	432.7 ± 180.1	363.8 ± 278.5 (n = 20)†	0.3850
γ-GT (0-26 U/L)	328.7 ± 218.3	340.1 ± 211.8	0.8762

*A p-value ≥ 0.05 indicates no statistical significance; †number of patients tested; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase.

Table 3. Immunological Parameters in AMA-Negative and -Positive Patients

Parameter (normal range)	AMA-negative patients (N = 15)	AMA-positive patients (N = 21)	*p**
IgM (40.2-167.5 mg/dl)	494.7 ± 256.5 (N = 12)†	533.4 ± 341.4 (N = 14)†	0.7429
γ-Globulin (0.8-1.6 g/dl)	2.2 ± 0.9 (N = 13)†	2.0 ± 0.5 (N = 18)†	0.4699
ANA positive (≥1:160)	11	8	0.0323
Homogenous	2	0	0.1667
Speckled	8	8	0.1792
Anti-centromere	1	2	0.4412
Anti-cytoplasmic	0	1	0.5833
Non-specific	1	0	0.4167
ASMA positive (≥1:20)	10 (n = 14)†	9 (n = 19)†	0.1129
HBsAg	0 (n = 13)†	0 (n = 18)†	1.0000
Anti-HCV	0 (n = 13)†	2 (n = 16)†	0.2956

*A p-value > 0.05 indicates no statistical significance; †number of patients tested; IgM, immunoglobulin M; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody.

bin between the 2 groups. Immunological data between AMA-negative and -positive patients are compared in Table 3. The positive rate for serum ANAs was higher in AMA-negative patients than in AMA-positive patients (73.3% vs. 38.1%, $p = 0.0323$). Among the immunofluorescence staining patterns of ANAs, the speckled type was commonly seen in both AMA-negative and -positive patients. However, none of these immunofluorescence staining patterns of ANA showed a difference between the 2 groups. There were no significant differences regarding serum IgM levels, γ-globulin levels, or the positive rate of ASMAs between the 2 groups. None of the histological findings significantly differed between these 2 groups (Table 4).

Thirty-one patients were tested for hepatitis B surface antigen (HBsAg), and 29 patients were tested for hepatitis C virus antibody (anti-HCV). None of these patients was HBsAg positive, and only 2 AMA-positive patients were anti-HCV positive.

Table 4. Histological Parameters in AMA-Negative and -Positive Patients

Parameter	AMA-negative patients (N = 15)	AMA-positive patients (N = 21)	*p**
Histological grading			
Stage 1	4	3	0.2175
Stage 2	5	8	0.2644
Stage 3	4	8	0.2219
Stage 4	2	2	0.3743
Specific histological parameters			
Granuloma	3	1	0.1622
Florid duct sign	1	1	0.2644
Ductless sign	4	6	0.2914
Positive copper stain	5	7	0.2790
Mallory bodes	0	1	0.5833
Fibrosis			
Portal-periportal	3	4	0.3262
Bridging	1	2	0.4412
Cirrhosis	2	2	0.3743

*A p-value > 0.05 indicates no statistical significance.

Of 15 patients who tested negative for serum AMAs at initial presentation, 11 (73.3%) repeatedly tested negative for serum AMAs (mean number of tests, 6.2; range, 3-10). Serum AMAs in the remaining 4 (26.7%) patients converted to positive (titer range 1:40 to 1:1280) during 10, 23, 47, and 56 (mean, 34) months of follow-up. None of the clinical, biochemical, immunological, or histological parameters of these 2 groups showed a statistically significant difference.

DISCUSSION

PBC should be suspected in a patient, particularly a woman, who complains of unexplained itching, fatigue, or jaundice. A diagnosis of PBC should be confirmed by liver biopsy, which will also provide information about the stage and the prognosis of the disease.[2] In our 36 patients who fulfilled the diagnostic criteria of PBC, 15 (41.7%) were not positive for serum AMAs at presentation. The rate of negative serum AMAs in PBC patients ranged from 4% to 10% in the majority of reports[1-4,14] but was up to 24% in a Taiwanese study.[6] The 41.7% (15/36) rate of negative AMAs at presentation in our series is higher than those published elsewhere. This may have been due to the fact that our patients were selected based on liver biopsies. In Taiwan, patients who are suspected of having PBC might refuse a liver biopsy especially when they test positive for AMAs. Such patients were not enrolled in this study. A high rate of negative serum AMAs in PBC patients was also seen in the other 2 studies, 32% in Goodman's report[8] and 44.1% (30/68) in Nakanuma's report.[16] In those 2 studies, patients were also included based on histological diagnosis.

The AMA test is highly sensitive and specific for diagnosing PBC. A positive test for AMAs is almost synonymous with PBC. To some extent, many published studies regarding PBC excluded patients without AMAs. In our study, we used the histopathologic features of the liver biopsy to define the disease, irrespective of the serum autoantibodies. Fluctuations in serum AMA titers are often observed during the course of PBC.[8,17] Flora et al. reported that 5 of 8 patients who were AMA negative and ANA positive were initially categorized as having AIC. These patients became AMA positive during follow-up. The authors thus proposed that AIC is an early variant of PBC.[7] In our study, 4 (26.7%) of 15 AMA-negative patients became AMA positive in a mean period of 34 months. According to our results (data not shown), the 4 AMA-seroconverted PBC patients and the remaining 11 AMA-negative PBC patients had the same clinical manifestations, liver biochemistries, serological features, and histological findings. This may imply that these 2 entities are likely the same disease with fluctuating AMA titers.

Our AMA-negative patients included significantly more asymptomatic patients ($p=0.0017$). Nakajima et al. reported that significantly more asymptomatic patients were found in AMA-negative PBC (or AIC).[18] They concluded that PBC patients in the early stage were more frequently included in their AIC group. PBC patients with negative serum AMAs had a higher prevalence of ANAs in previous reports. For example, ANAs were present in 93%,[6] 79%,[3] and 63%[8] of AMA-negative PBC patients compared with 66%,[6] 33%,[3] and 54%,[8] respectively, of AMA-positive patients in different studies. Consistently, a higher rate of positive ANAs (73.3% vs. 38.1%, $p=0.0323$) was also seen in AMA-negative patients in this study. ASMAs were more prevalent in AMA-negative patients in most but not all previous reports.[3,4,6,12,18] In our results, the positive rate of serum ASMAs in the AMA-negative group was higher (71.4% vs. 47.4%, $p=0.1129$) but not statistically significant. Serum IgM levels tend to be lower in AMA-negative patients.[3-4,6,12,18] In the present study, serum IgM in the AMA-negative group was only slightly lower than that in the AMA-positive group (494.7 ± 256.5 vs. 533.4 ± 341.4, respectively, $p=0.7429$). This might have been due to data on IgM of too few subjects in the AMA-positive group being collected for analysis.

All of the 36 patients were treated with ursodeoxycholic acid during follow-up. The mean period of follow-up was 65.3 ± 38.8 (range, 12-156) months in the AMA-negative group and 56.7 ± 45.9 (range, 3-156) months in the AMA-positive group. Three of 15 (20.0%) AMA-negative patients and 6 of 21 (28.6%) AMA-positive patients had ultrasonic diagnosis of liver cirrhosis when PBC was initially diagnosed. Five of the remaining 12 (41.7%) AMA-negative patients and 5 of the 15 (33.3%) AMA-positive patients developed liver cirrhosis (diagnosed by ultrasound) after 65.0 ± 48.2 (range, 8-130) months and 49.0 ± 51.8 (range, 6-126) months of follow-up,

respectively. However, there were no significant differences between the AMA-negative and -positive groups with regard to the mean period of follow-up, number of patients with liver cirrhosis at presentation or during follow-up, or the mean period for the development of liver cirrhosis during follow-up.

The presence of serum ANAs and ASMAs raises the question of autoimmune hepatitis (AIH), especially in AMA-negative PBC patients. AIH is characterized by the presence of interface hepatitis on histological examination. Cholestatic clinical, laboratory, and histological changes preclude the diagnosis.[19] All of our AMA-negative PBC patients had liver biochemical tests for a cholestatic picture, and all of the patients received a liver biopsy, but none had histopathologic features suggestive of AIH. We believe that AIH was unlikely in our AMA-negative group.

The prevalence of hepatitis B virus (HBV) infection is high in Taiwan, with an HBsAg carrier rate of 15%-20% in the general population.[20] However, 13 of 15 AMA-negative patients and 18 of 21 AMA-positive patients in this study were negative for HBsAg. Our results are consistent with previous reports in Taiwan.[6,21-22] PBC patients in Taiwan had a low prevalence of HBV infection, regardless of whether they were AMA negative or positive. Possible reasons were proposed by Chien et al.[21] but demand further investigation.

It was suggested that serum anti-HCV positivity did not influence the clinical presentation or course of PBC.[23] Rowan et al. even questioned whether the hepatitis C virus is an etiological agent or an artifact in PBC.[24] In their study, seropositivity of anti-HCV in 96 PBC patients was 31% tested by the first-generation enzyme immunoassay (EIA1), 14% by EIA2, and 0% by EIA3. However, cases of chronic hepatitis C associated with PBC, with and without being positive for AMAs, have recently been reported.[25] In this study, only 2 in 16 AMA-positive patients were positive for anti-HCV. Both patients had their seropositivity for anti-HCV tested by all 3 generations of EIA during follow-up. The significance of this result is not clear.

Goodman et al. classified their PBC patients into the 4 groups of AMA positive/ANA positive, AMA positive/ANA negative, AMA negative/ANA positive, and AMA negative/ANA negative.[8] According to their results, there were no significant differences in gender, hepatic histopathology, or other laboratory tests between these 4 groups. In addition, Masuda et al. reported an interesting case of PBC that was initially positive for serum AMAs but negative for ANAs.[26] These 2 antibodies fluctuated independently and showed all 4 serological patterns as described by Goodman et al.[8] during follow-up. The authors suggested that a diagnosis of PBC or AIC might depend on the different 'phase' of the same disease in some cases. Not only did our AMA-negative patients have seroconversion of AMAs, but also 1 (4.8%) of our AMA-positive patients became AMA negative after 108 months of follow-up.

There have been many studies regarding the clinicopathological features of AMA-negative PBC patients based on immunofluorescence-tested AMA. A majority of these features are known to be similar between AMA-negative and -positive PBC patients. The present study can confirm those previous findings. In conclusion, patients with AMA-negative PBC tend to be asymptomatic and ANA positive. Some patients may become positive to AMAs during follow-up. Our results imply that AMA-negative PBC might be a variant of AMA-positive PBC, rather than a separate disease.

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抗粒線體抗體陰性之原發膽道性肝硬化：長庚紀念醫院之經驗

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背 景： 雖然部分患者在臨床，組織學及實驗室檢查方面具有原發膽道性肝硬化的特徵但是卻缺乏血清抗粒線體抗體。在亞洲國家，關於抗粒線體抗體陰性之原發膽道性肝硬化的臨床資料仍相當有限。因此於本研究報告中，我們檢視本院抗粒線體抗體陰性之原發膽道性肝硬化患者的資料以期對此情況有更進一步的了解。

方 法： 自西元1985年至2000年，在林口長庚醫院共有36位患者經病理診斷爲原發膽道性肝硬化。其中15例第一次檢驗其血清抗粒線體抗體呈陰性，另21例則爲陽性。我們分析比較血清抗粒線體抗體陰性和陽性這兩組病患的臨床表現，肝生化指數，血清免疫標記，和組織學特徵的異同。

結 果： 抗粒線體抗體陰性和陽性兩組原發膽道性肝硬化患者只存在著些許不同。與抗粒線體抗體陽性患者比較，抗粒線體抗體陰性組明顯有較多的無症狀患者 ($p=0.0017$)，較高的血清抗核抗體陽性率 ($p=0.0323$)。除此之外，其它的臨床表現，肝生化指數，血清免疫標記，和組織學特徵並無有意義的差別。值得注意的是，15位抗粒線體抗體陰性患者中有4位在追蹤10, 23, 47以及56月 (平均34月) 時其血清抗粒線體抗體轉爲陽性。

結 論： 抗粒線體抗體陰性之原發膽道性肝硬化患者傾向於較無症狀,且血清抗核抗體呈陽性。部分患者於後續追蹤時其血清抗粒線體抗體可轉爲陽性。我們的資料暗示著抗粒線體抗體陰性原發膽道性肝硬化是抗粒線體抗體陽性之原發膽道性肝硬化的一種變異，而非另一種不同的疾病。

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關鍵字： 原發膽道性肝硬化，抗粒線體抗體，抗核抗體。

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