Digestive Diseases and Sciences, Vol. 31, No. 7 (July 1986), pp. 705–711

Frequency and Significance of Antimitochondrial Antibodies in Severe Chronic Active Hepatitis

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Of 187 patients with severe chronic active hepatitis, 37 (20%) had antimitochondrial antibodies, usually of low titer (≤1:40). To assess the significance of this finding and to identify differentiating features from primary biliary cirrhosis, 24 of these patients were compared to two groups of matched counterparts of which one lacked antimitochondrial antibodies and one had the antibodies together with typical primary biliary cirrhosis. Higher serum levels of alkaline phosphatase and an increased frequency of stainable hepatic copper were the only features that distinguished these patients from those without antimitochondrial antibodies. The response to corticosteroids was not influenced by antibody status. Histologic interpretation differentiated primary biliary cirrhosis from antibody-positive chronic active hepatitis in 91% of instances. High antibody levels (≥1:160), immunoglobulin M concentrations (≥6.0 mg/ml), alkaline phosphatase activity (≥ fourfold normal), and cholesterol elevations (≥300 mg/dl) separated the syndromes in 82% of instances. Patients with laboratory features of primary biliary cirrhosis but histologic findings of chronic active hepatitis responded to corticosteroids. We conclude that low titers of antimitochondrial antibodies are common in chronic active hepatitis, and the presence of these antibodies does not preclude a satisfactory response to corticosteroids. Histologic features are more reliable than biochemical findings in differentiating the syndromes and should be the basis for diagnosis and treatment.

Typically, chronic active hepatitis (CAH) is a syndrome characterized by clinical and biochemical manifestations of chronic parenchymal inflammation and histologic findings of periportal (piecemeal) necrosis (1). In contradistinction, the primary biliary cirrhosis (PBC) syndrome is characterized by clinical and biochemical manifestations of cholestatic hepatobiliary disease and histologic evidence of inflammatory destruction of interlobular bile ducts (2, 3). The two disorders can usually be distinguished without difficulty (3, 4). Occasionally, however, the syndromes may resemble each other and diagnostic uncertainty may delay proper therapy (5). Clinical and biochemical features of cholestasis are present in as many as 50% of patients with CAH, and these findings may predominate in up to 20% of cases (6). Additionally, bile duct lesions that can be misinterpreted as representing PBC may be recognized in the liver tissue of 12% of patients who have met established criteria for the diagnosis of CAH (2, 5, 7–9).

Manuscript received December 19, 1984; revised manuscript received October 1, 1985; accepted October 21, 1985.

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Presented in part at the national meeting of the American Gastroenterological Association, May 25, 1983, Washington, D.C.

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0163-2116/86/0700-0705$05.00/0

Characteristic patterns of laboratory abnormalities have been described for CAH and PBC (10), but cluster analysis has shown that these patterns do not confidently distinguish the diseases (11). In patients with PBC, the serum levels of gamma glutamyltransferase, alkaline phosphatase, haptoglobin, ceruloplasmin, cholesterol, and immunoglobulin M (IgM) are higher than in patients with CAH, and the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and immunoglobulin G (IgG) are lower (10). Patients with CAH have a greater frequency of smooth muscle antibody (SMA) positivity and antinuclear antibody (ANA) reactivity than patients with PBC and a lower frequency of antimitochondrial antibody (AMA) detection (10). No specific immunoserologic or laboratory pattern, however, is pathognomonic of either disorder, and the presence of clinical, biochemical, and histologic features that are shared by both syndromes has led to speculation that these disorders may represent different manifestations of a single autoimmune process (12) or that mixed forms of the syndromes may exist as distinct entities (13, 14). This latter possibility is supported by the identification of antimitochondrial antigens that may be disease specific (13–15).

In this report, we describe a group of patients with features of CAH who have antimitochondrial antibodies, and we assess the significance of AMA positivity in these patients by comparing their laboratory findings, histologic features, and prognosis with those of AMA-negative counterparts. Additionally, we compare these patients with those who satisfy conventional criteria for PBC to identify differentiating features.

MATERIALS AND METHODS

Of 187 patients fulfilling previously established criteria for severe CAH and enrolled in a prospective treatment trial (16), 37 (20%) presented with a positive test for serum AMA. AMA had been sought in all patients using rat kidney sections and anti-human IgG-specific fluorescein-labeled rabbit or goat gamma globulin (17). A 1:5 screening dilution of patient sera was used, and all positive sera were diluted serially to determine the antibody titer. Four AMA-positive patients were excluded because one had HBsAg and three had been randomized to placebo therapy during the initial controlled phase of the Mayo trial (1967–1971) and could not be assessed for corticosteroid response (18).

Histologic stage at presentation, corticosteroid treatment regimen, sex, and age were used to match the remaining patients with AMA to patients from the same treatment trial who had disease of comparable severity but absence of AMA. Radioimmunoassay (Abbott Laboratories, North Chicago, Illinois) of fresh or frozen (−20° C) serum specimens obtained from each patient at accession was utilized to confirm the absence of HBsAg and immunoglobulin M antibody to the hepatitis A virus. All patients with and without AMA denied homosexual contact, illicit drug use, and receipt of blood transfusion within one year of disease onset.

The AMA-positive patients were also matched according to histologic stage at presentation, sex, and age to patients enrolled in a prospective, placebo-controlled trial assessing D-penicillamine in the management of PBC (19). Participation in the D-penicillamine trial required that patients have AMA positivity (titer ≥1:10), more than threefold elevation of serum alkaline phosphatase activity, and histologic features which satisfied previously published criteria for PBC (20, 21).

The liver biopsy specimens in both the PBC and CAH programs were studied under coded identification. Presence of destructive granulomatous cholangitis (4) was considered diagnostic for PBC. Absence or decrease in the number of interlobular and septal bile ducts, and the presence of cholestatic features such as periportal feathery degeneration (cholate stasis), periportal accumulation of copper and copper protein, and periportal cholestasis were considered suggestive of PBC. CAH was diagnosed if specimens showed periportal hepatitis without ductal abnormalities or with proliferation of bile ducts, if cholestatic features as previously described were absent, and particularly if multilobular necrosis was found. Other features such as piecemeal necrosis or lymphoid, pleomorphic, and fibrous cholangitis (4) were considered to have little discriminating value.

For the purposes of histologic matching between patients in the CAH and PBC trials, the morphologic finding of periportal necrosis was matched with PBC, stage II; bridging and multilobular necrosis was matched with PBC, stage III; and active cirrhosis was matched with PBC, stage IV (21). Previous evaluation of observer error and sampling variability had documented the accuracy of percutaneous needle biopsy interpretation in assessing the type and degree of hepatic inflammation, although only a minimal occurrence of cirrhosis could be determined in this fashion (22).

Twenty-four AMA-positive patients from the CAH study were matched successfully to 24 AMA-negative patients from the same study and 24 AMA-positive patients from the PBC trial. These 72 patients comprise the basis of this report. Nineteen patients in each study group were female. The mean age of AMA-positive patients from the CAH study was similar to that of patients from the PBC study (mean 48 ± 3 years versus 52 ± 2 years) but was significantly different from that of AMA-negative patients from the CAH study despite our attempt to match to the nearest age (mean 48 ± 3 years versus 38 ± 3 years, $P < 0.05$). In each group, six patients had periportal necrosis (or PBC, stage II); 12 patients had bridging or multilobular necrosis (or PBC, stage III); and six patients had active cirrhosis (or PBC, stage IV). Nine patients with AMA who satisfied criteria for severe CAH could not be matched with AMA-negative counterparts

and patients from the PBC trial, and they were excluded from the analysis.

Complete evaluations were made in all patients at entry and at regular intervals thereafter. Patients in the CAH groups were assessed every six months during treatment and for at least one year after cessation of therapy. Patients in the PBC group were examined at annual intervals. Routine laboratory (serum AST, bilirubin, albumin, alkaline phosphatase, gamma globulin, prothrombin, cholesterol, and immunoglobulin levels) and serologic (AMA, SMA, ANA) tests were done during each visit. Hepatic tissue was procured by percutaneous transthoracic or subcostal biopsy using the modified Vim-Silverman or Jamshidi needle at accession and at annual intervals. To reassess intraobserver variation, the hepatic tissue specimens obtained at accession were reinterpreted under code. Rhodanine stains for copper (23) were available in 66 of the 72 cases.

Patients from the CAH program were treated in accordance with one of three possible treatment protocols (24). In each of the two CAH groups, 13 patients received prednisone, 10 mg daily, in conjunction with azathioprine, 50 mg daily; seven received prednisone alone, 20 mg daily; and four received prednisone on alternate days (mean dose, 20 mg every other day; range, 10–50 mg) with the dose titrated to maintain normal serum AST levels. Patients in the PBC group received either placebo or D-penicillamine (1 g daily). Treatment was continued until previously reported clinical, biochemical, and histologic criteria for remission, treatment failure, or drug toxicity had been satisfied (16, 24). Remission was diagnosed if symptoms disappeared, serum AST level improved to less than twofold normal, other laboratory tests (serum bilirubin and gamma globulin levels) normalized, and histologic appearance improved to normal, minimal inflammatory activity, or cirrhosis with little or no inflammatory change.

The 24 patients in each study group were compared and differences in laboratory and histologic findings at presentation were sought. The reproducibility of histologic interpretation was assessed, and differences in prognosis between AMA-positive and AMA-negative patients who received corticosteroids were evaluated. Chi-square analysis with Yates' correction was used to compare dichotomous variables, and the unpaired *t* test was used to evaluate the significance of differences in means for continuous variables. Data are presented as mean ± SEM in tables and text.

RESULTS

Laboratory Findings at Presentation. Patients selected from the CAH study with AMA positivity had a higher serum alkaline phosphatase level at presentation than AMA-negative counterparts (Table 1). Other biochemical and serologic findings, however, were similar between the two groups. AMA-positive patients from the PBC trial had higher serum levels of alkaline phosphatase, cholesterol, IgM, and albumin than patients from the CAH program and lower serum levels of AST and IgG (Table 1). The laboratory abnormalities in the AMA-positive patients from the CAH group tended to be intermediate between those of their AMA-negative and PBC counterparts (Table 1).

Histologic Findings at Presentation. The reinterpretation of the liver biopsy specimens under code agreed with the initial interpretation in 65 of 72 instances (90%). The reproducibility was complete in the AMA-negative patients (23 of 23 instances) and was 91% in the AMA-positive patients (42 of 46 instances). In three cases, the liver tissue sample was considered inadequate for reinterpretation. In two cases, histologic findings originally interpreted as compatible with PBC were reinterpreted as compatible with CAH. In two other cases, the original histologic diagnosis of CAH was changed to PBC after repeat examination. AMA-positive patients

TABLE 1. LABORATORY FINDINGS AT PRESENTATION*

	AMA⁻ CAH (N = 24)	P	*AMA⁺ CAH* (N = 24)	P	*PBC* (N = 24)
AST (nl: ≤27 units/liter)	686 ± 96		484 ± 88	0.001	73 ± 6
Bilirubin (nl: ≤1.1 mg/dl)	5.4 ± 1.2		5.8 ± 1.3		3.1 ± 1.0
Alkaline phosphatase (actual/normal)†	1.3 ± 0.2	0.02	2.6 ± 0.5	0.001	5.8 ± 0.7
Albumin (nl: ≥3.1 g/dl)	3.0 ± 0.1		2.9 ± 0.2	0.01	3.5 ± 0.2
Gamma globulin (nl: ≤1.6 g/dl)	3.6 ± 0.2		3.3 ± 0.2	0.001	1.9 ± 0.2
Cholesterol (mg/dl)	199 ± 13		217 ± 21	0.01	335 ± 27
IgG (nl: ≤14.3 mg/ml)	32.6 ± 3.1		29.7 ± 1.6	0.001	19.1 ± 1.9
IgM (nl: ≤1.4 mg/ml)	2.5 ± 0.3		4.8 ± 1.3	0.02	5.9 ± 0.8
IgA (nl: ≤3.0 mg/ml)	3.1 ± 0.3		2.7 ± 0.2		2.2 ± 0.2
Antinuclear antibody ≥1:40 *(N)*	10		10		ND
Smooth muscle antibody ≥1:40 *(N)*	13		11		ND

*AMA = antimitochondrial antibody; CAH = chronic active hepatitis; PBC = primary biliary cirrhosis; AST = serum aspartate aminotransferase level; IgG = immunoglobulin G; IgM = immunoglobulin M; IgA = immunoglobulin A; nl = normal; ND = not determined.
†Actual determination divided by upper limit of normal range.

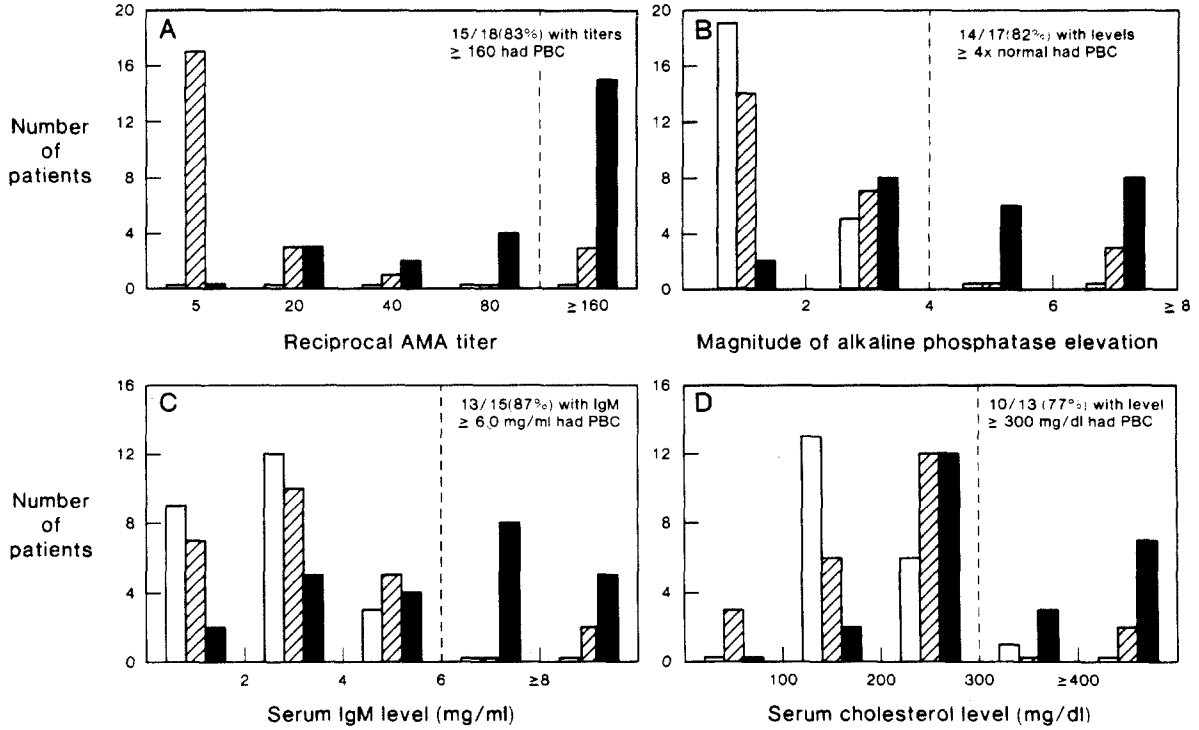

Fig 1. Frequency distribution of serum antimitochondrial antibody (AMA) titer (panel A), alkaline phosphatase elevation (panel B), immunoglobulin M (IgM) concentration (panel C), and cholesterol level (panel D) in patients with AMA-negative chronic active hepatitis (clear bar), AMA-positive chronic active hepatitis (hatched bar), and primary biliary cirrhosis syndrome (solid bar). The serum alkaline phosphatase value represents the actual determination divided by the upper limit of the normal range.

from the CAH trial could not be distinguished from AMA-negative counterparts by routine histologic assessment.

Of 22 AMA-negative patients in whom the rhodanine stain for tissue copper was available, none had positive stains. Of 44 tissue samples obtained from the AMA-positive patients (21 from the CAH program and 23 from the PBC trial), 22 were positive for copper. The rhodanine stain for tissue copper differentiated the AMA-negative from the AMA-positive patients (0% versus 50%, $P < 0.001$). Eighteen of the 23 patients from the PBC trial in whom tissue sampling was possible had positive liver copper stains compared to 4 of 21 AMA-positive counterparts from the CAH program (78% versus 19%, $P < 0.001$). The liver tissue from the AMA-positive patients with histologic features of CAH was stainable for copper more commonly than the AMA-negative counterparts (19% versus 0%, $P < 0.05$).

Distinguishing Features. Patients with histologic features of PBC tended to have markedly elevated serum levels of AMA, alkaline phosphatase, IgM, and cholesterol which distinguished them from the majority of AMA-positive counterparts with histologic features of CAH (Figure 1). Patients from the CAH study infrequently had AMA titers that were greater than the screening dilution of 1:5 (Figure 1A) and only three of these (12%) had titers that exceeded 1:160 (highest titer, 1:1280). Of the 18 patients with AMA titers of at least 1:160, 15 (83%) had histologic features of PBC (Figure 1A). The highest AMA titer among these patients was 1:10,240. None of the AMA-negative patients had alkaline phosphatase elevations of more than four-fold normal, and only three of the AMA-positive patients with histologic findings of CAH (12%) had elevations of this degree (Figure 1B). Although 30 of the 48 patients (62%) with CAH had serum IgM levels that exceeded the normal limit of 1.4 mg/ml, only two AMA-positive patients from this group had serum levels that exceeded 6.0 mg/ml. Of the 15 patients with serum IgM levels of greater than 6.0 mg/ml, 13 (87%) had histologic findings of PBC (Figure 1C). Serum cholesterol concentrations of more than 300 mg/dl provided a similar differentiation (Figure 1D). High serum levels of AMA (≥1:160), IgM (≥6.0 mg/ml), alkaline phosphatase

(≥ fourfold normal), and cholesterol (≥300 mg/dl) correlated with the histologic diagnosis of PBC in 52 of 63 instances (82%).

Disease Outcome. Corticosteroid-treated patients with and without AMA-positivity behaved similarly during comparable periods of treatment (Table 2). Cirrhosis, ascites, encephalopathy, and esophageal varices developed with similar frequency in both study groups, and death from hepatic failure occurred as commonly during similar periods of observation (Table 2). None of the AMA-positive patients in the D-penicillamine treatment trial improved sufficiently to satisfy remission criteria during 58 ± 33 months of follow-up (range 12–118 months) and seven of the 24 patients died of liver failure.

Eight AMA-positive patients from the CAH study had positive hepatic tissue copper staining or markedly abnormal serum levels of AMA (titer ≥ 1:160), alkaline phosphatase (greater than fourfold normal), IgM (greater than 6.0 mg/ml), cholesterol (greater than 300 mg/dl), or various combinations of these (Figure 2). In two patients, the histologic findings at accession which had been interpreted as consistent with CAH were reinterpreted as consistent with PBC (Figure 2). Seven of these patients improved sufficiently during corticosteroid therapy to satisfy criteria for remission; one other improved during therapy but not sufficiently as yet to fulfill remission criteria.

TABLE 2. PROGNOSIS OF PATIENTS WITH AND WITHOUT AMA*

	AMA⁻ CAH (N = 24)	*AMA⁺ CAH* (N = 24)	*PBC* (N = 24)
Treatment results *(N)*			
Remission	19	17	0
Treatment failure	4	4	NA
Drug toxicity	0	1	6
Continued treatment	1	2	11
Duration treatment (months)	23 ± 4	20 ± 3	58 ± 33
Complications *(N)*			
Ascites	4	3	4
Coma	2	3	1
Cirrhosis	5	7	10
Varices	2	4	10
Death (from liver disease)	3	1	7
Duration follow-up (months)	84 ± 9	68 ± 7	58 ± 33

*AMA = antimitochondrial antibody; CAH = chronic active hepatitis; PBC = primary biliary cirrhosis; NA = not applicable.

DISCUSSION

Our study indicates that 20% of patients who satisfy established biochemical and histologic criteria for severe CAH have antimitochondrial antibodies. Although the majority of these patients (88%) have low titers of AMA (≤1:40), suggesting that the reaction is nonspecific, higher serum levels of alkaline phosphatase and an increased frequency of stainable copper in liver tissue indicated a greater degree of cholestasis in these patients than in AMA-negative counterparts. Other laboratory and histologic findings, however, failed to distinguish these patients, and prognosis after corticosteroid therapy was similar in individuals with and without AMA. Previous studies have emphasized that AMA, as detected by fluorescein-labeled rabbit antihuman IgG, is neither organ nor species specific, and AMA positivity has been described in various cholestatic liver diseases and collagen disorders (13–15). Our findings corroborate the lack of specificity of AMA positivity for PBC, especially in low titer. Low levels of AMA are not uncommon in patients with CAH, and the presence of AMA, regardless of titer, in patients with histologic features of CAH does not preclude a satisfactory response to corticosteroids.

AMA-positive patients with histologic features of PBC were usually distinguishable from other AMA-positive patients by liver biopsy interpretation and assessment of tissue copper staining. Although histologic findings were inconclusive in 9% of instances and positive tissue copper staining occurred in 19% of patients with CAH, the morphologic assessment was more reliable than the laboratory findings in differentiating PBC from CAH. Only the degree of laboratory abnormality separated the syndromes and commonly reflected the histologic findings. AMA titers of at least 1:160, serum IgM concentrations that exceeded 6.0 mg/ml, serum alkaline phosphatase levels of at least fourfold normal, and blood cholesterol concentrations ≥300 mg/dl were associated with histologic evidence of PBC in more than 80% of instances.

Eight of the 24 AMA-positive patients from the CAH program (33%) had such severe cholestatic laboratory features that a confident diagnosis was not possible. In two such patients, the histologic interpretation of CAH was not reproducible. Patients with mixed features of PBC and CAH have been described previously (5, 7, 8, 13, 14) and our patients may have represented a hybrid syndrome.

Patient	Histologic features of PBC	AMA titer ≥1:160	Alkaline phoshatase ≥4x normal	IgM ≥6.0 mg/ml	Cholesterol ≥300 mg/dl	Copper stain pos.	Steroid response
#1	✓	✓		✓			remission
#2	✓		✓			✓	remission
#3		✓		✓			remission
#4		✓	✓			✓	remission
#5			✓		✓		remission
#6						✓	remission
#7						✓	remission
#8					✓		cont. treatment

Fig 2. Findings and response to corticosteroid therapy of antimitochondrial antibody (AMA) positive patients from the chronic active hepatitis program who had inconclusive histologic features or atypical laboratory findings.

Previous reports have indicated that the response to corticosteroid therapy may differentiate CAH with cholangitic features from PBC (5). In our study, all patients with an inconclusive diagnosis improved during corticosteroid therapy, and seven experienced remission of their disease. Unfortunately, we do not know the prognosis of these overlap cases untreated. Our previous experience, however, with untreated CAH of similar severity (16) and our follow-up in this study of PBC of comparable histologic stage would indicate that spontaneous improvement to this degree is unusual. Since diagnostic confusion resulted mainly from laboratory rather than histologic findings which reflected severe cholestasis, our experience emphasizes the importance of an accurate histologic interpretation in differentiating cholestatic CAH from PBC. Patients with morphologic features of CAH should be diagnosed and treated as such despite laboratory findings which suggest PBC.

Unfortunately, we were unable to estimate how many patients with histologic features of PBC have clinical and laboratory findings suggestive of CAH, and the response of these patients to corticosteroid therapy remains unknown. Our selection criteria for PBC required predominance of cholestatic rather than inflammatory features, and the diagnosis of PBC precluded the use of corticosteroids. Nevertheless, clinical, biochemical, and histologic improvements after corticosteroid therapy have been described in selected patients with morphologic findings of PBC and clinical features of active hepatocellular inflammation (5, 25), and the two patients in our study whose original histologic diagnosis of CAH was changed to PBC after reinterpretation did enter remission after corticosteroid treatment. These observations justify further controlled assessment of corticosteroids in the management of such patients.

Clearly, better methods than those currently available are necessary to identify patients with mixed histologic features who may be responsive to corticosteroid therapy, and the recent recognition of disease-specific mitochondrial antigens and antibodies may facilitate this differentiation (13–15). In contrast to patients with PBC who possess a PBC-specific antimitochondrial antibody directed against a trypsin-sensitive antigen on the inner mitochondrial membrane, patients with mixed features have a second mitochondrial antibody directed against a trypsin-insensitive antigen on the outer membrane (13–15). Although the patterns of antimitochondrial antibody immunofluorescence in rat kidney and liver have correlated closely with histologic features of PBC and CAH, these findings have not been correlated with disease behavior or treatment response. Such a correlation might provide a more confident guideline for therapy in the future.

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