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Are bile duct lesions of primary biliary cirrhosis distinguishable from those of autoimmune hepatitis and chronic viral hepatitis? Interobserver histological agreement on trimmed bile ducts

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Background. Primary biliary cirrhosis (PBC) is histopathologically characterized by chronic nonsuppurative destructive cholangitis and ductopenia of interlobular bile ducts. Bile duct injury is also often encountered in chronic viral hepatitis (CVH) and in autoimmune hepatitis (AIH). ***Methods.*** In this study, we performed interobserver agreement analysis on 90 injured bile ducts from liver specimens of PBC (17 cases), CVH (26 cases), and AIH (18 cases), with 30 bile ducts chosen from each disease group. Digital images of bile ducts with minimal periductal elements were recorded in CD-ROM format and sent to 14 observers (six special hepatopathologists, four local hepatopathologists, and four general pathologists). We analyzed the following issues: (1) diagnostic accuracy of PBC, based only on bile duct lesions; (2) classification of bile duct lesions in AIH cases as destructive cholangitis equivalent to PBC-associated injury, or not. ***Results.*** The diagnostic accuracy of PBC cases with severe bile duct injuries was very high (over 80%), although the accuracy in cases with only mild bile duct injuries was low (50% or less). For AIH, each observer classified 9 of the 30 bile ducts, on average, as destructive cholangitis. ***Conclusions.*** This study revealed that 66.9% of PBC cases could be diagnosed based on trimmed bile ducts alone. Bile duct injury similar to that in PBC could be encountered in AIH.

Key words: overlap syndrome, chronic nonsuppurative destructive cholangitis, antimitochondrial antibodies, autoimmune cholangitis

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Introduction

Primary biliary cirrhosis (PBC) is characterized by chronic nonsuppurative destructive cholangitis (CNSDC), granuloma formation, and progressive and extensive loss of the bile duct.[1,2] Its diagnosis is dependent on clinical history, laboratory data, and histological evaluation.[3] Histological findings are thought to be useful for the diagnosis of PBC. However, histological diagnosis of liver biopsy specimens is sometimes difficult or arbitrary because the degree of bile duct injury in PBC varies from CNSDC to nonspecific duct injuries, and the distribution of diagnostic lesions (CNSDC) is heterogeneous in the liver, causing sampling errors.

Chronic viral hepatitis (CVH), particularly when it is hepatitis C virus (HCV)-related, is not infrequently associated with bile duct injury, which is called hepatitis-associated bile duct lesion.[4] In CVH, the degree of bile duct injury is mild in general, although striking duct injuries are encountered occasionally. However, even those cases with striking duct injuries are easily differentiated from PBC clinicopathologically, because the

clinicopathological features of CVH are quite different from those of PBC, and, in CVH, hepatitis viral markers are positive and the concomitant occurrence of histological features of CVH is always seen in liver biopsy specimens.

Autoimmune hepatitis (AIH) cases with typical clinical and histopathological features are easily diagnosed, although the differentiation of AIH from PBC is difficult in some cases, because the clinicopathological features in both diseases are similar or may overlap, and PBC patients frequently show the histological features of hepatitic parenchymal and periportal changes, in addition to cholestatic and cholangitic lesions.[5] In addition, focal bile duct injury has been reported in liver biopsy specimens from AIH patients.[6] Furthermore, so-called overlap syndrome has also been proposed for cases with features of both PBC and AIH at several institutions.[7–10] Based on these issues, the histological evaluation and estimation of bile duct change is very important for the differentiation of PBC from AIH with bile duct injuries. In fact, the presence or absence of biliary damage resembling CNSDC is one of the important findings in the diagnostic criteria of AIH proposed by the International Autoimmune Hepatitis Group.[11]

In this study, we examined interobserver agreement in the histological evaluation of bile duct changes associated with PBC, CVH, and AIH. The purpose of this study was to reveal the histological differences in bile duct lesions associated with these diseases.

Materials and methods

Observers

The observers were 14 medical doctors (K.H., M.S., K.T., J.H., S.S., S.M., K.Y., M.N., K.S., M.K., N.K., A.U., Y.K., and K.M.). These observers were categorized into three groups: special hepatopathologists (S.S., S.M., K.Y., M.N., K.S., M.K.), local hepatopathologists (K.H., M.S., K.T., J.H.), and general pathologists (N.K., A.U., Y.K., K.M.). These three groups were defined as follows. Special hepatopathologists who had been engaged in hepatology and hepatopathology for more than 20 years in their careers. They received liver specimens for consultation from everywhere in Japan. They had observed liver specimens from more than 100 cases a year for medical practice and medical research. Local hepatopathologists were pathologists working in the Hokuriku area in Japan. They had been engaged in research on hepatopathology for more than 10 years. They experienced approximately 50 new cases of liver diseases a year. They were members of the Japanese Society of Pathology and the Japanese Society of Hepatology. General pathologists were working as general pathologists not specializing in hepatopathology. The special hepatopathologists were thought to have more experience in hepatopathology than the local hepatopathologists, who, in turn, were more trained in hepatopathology than general pathologists. No observer participated in the case selection or in the process of making bile duct images.

Case selection

Seventeen cases of PBC, 26 cases of CVH, and 18 cases of AIH, all of which had bile duct injury histologically, were selected from the files of Kanazawa University Hospital and the Department of Human Pathology, Kanazawa, Japan, from 1993 through 2002. The male/female ratio, average age, histological stage, and degree of bile duct injury of patients in each disease group are shown in Table 1. All cases were in adults. The diagnosis of PBC, CVH, or AIH was done clinicopathologically, as follows. In all the PBC cases, the patients were serologically positive for antimitochondrial antibodies (AMA); 10 cases histologically showed CNSDC, 4 cases showed epithelioid granuloma, and all 17 cases showed bile duct injury, such as loss of polarity of the biliary epithelia, narrowing of the bile duct lumen, and irregularity in the size of the nuclei of the biliary epithelia. Twenty-three patients and 3 patients with CVH were serologically positive for HCV antibody and hepatitis B surface (HBs) antigen, respectively, and all 26 cases histologically showed chronic hepatitis with variable fibrosis and necroinflammation. All AIH patients had antinuclear antibody (ANA; titer, 40–1280 in serum, and all cases corresponded to the "definite" or "probable" scorings proposed by the International AIH Group.[11] Liver biopsies, all performed before steroid therapy, showed chronic active hepatitis. All the AIH patients were negative for AMA, and overlap syndrome of PBC/AIH was not included in this study. None of the PBC and AIH patients had serological markers for HCV or HBV. The scoring for the staging (fibrosis score: 1, 2, 3, and 4) of chronic hepatitis proposed by the International Study Group[12] was adopted as the scoring system for CVH and AIH, and the staging of PBC was estimated based on the staging system of Schener and Lefkowitch[13] (stage 1, 2, 3, and 4).[13] These two staging systems were not the same in regard to the scoring, but seemed to be comparable to each other. The scores are shown in Table 1.

Processing of liver tissue specimens

Thirty bile ducts with various degrees of biliary epithelial damage were randomly selected from each of the three above disease groups by two authors (Y.Z. and

Table 1. Numbers of cases, average age of the patients, male/female ratio, histological stage, and the degree of bile duct injury in primary biliary cirrhosis, chronic viral hepatitis, and autoimmune hepatitis

	Number of cases	Average age (years)	Male/ female (ratio)	Stage				Bile duct injury (30 bile ducts)		
				1	2	3	4	Mild	Moderate	Severe
PBC	17	55.2	1:16	8	8	1	0	13	12	5
CVH	26	52.1	11:15	8	5	7	6	17	11	2
AIH	18	52.1	4:14	1	5	7	5	12	15	3

Stages 1, 2, 3, and 4 for PBC by Scheuer's staging, and stages 1, 2, 3, and 4 for CVH and AIH by Desmet's staging
PBC, primary biliary cirrhosis; CVH, chronic viral hepatitis; AIH, autoimmune hepatitis

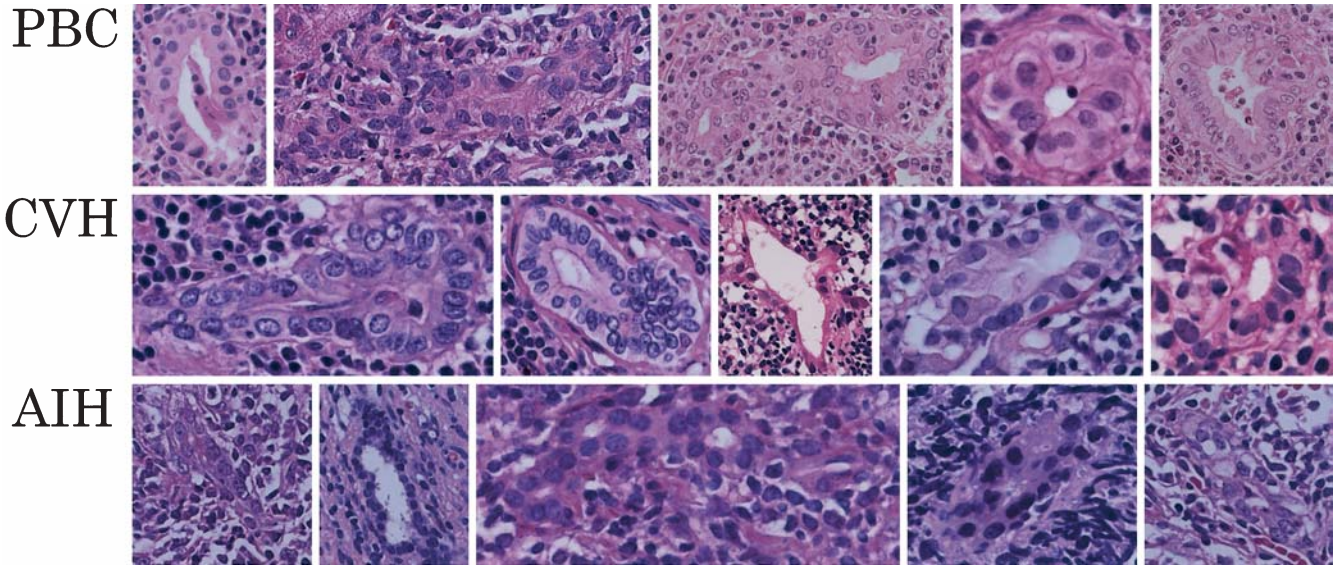

Fig. 1. Five examples of bile duct lesions from each disease group: primary biliary cirrhosis (*PBC*); chronic viral hepatitis (*CVH*); and autoimmune hepatitis (*AIH*). Digital images were recorded at a magnification of ×400, and the images were cut out squarely, using computer software

Y.N.). The bile ducts showed a loss of polarity of the biliary epithelia, acidophilic change of the biliary epithelia, inconspicuous bile duct lumen, and intraepithelial lymphoid infiltration. A maximum of 4 bile ducts were selected from one case. These bile ducts were collected as digital images, and the images were cut out squarely using a computer image-analyzing system. Periductal areas of the specimens were excluded as much as possible (so that trimmed bile ducts were obtained). Fifteen examples of processed bile duct images (five examples from each disease group) are shown in Fig. 1.

Design of the study

In this study, only digital images, and not clinical history or laboratory data, were available for all the observers. Digital images of the bile ducts were recorded on CD-ROM, which was sent to each observer with a questionnaire covering the following items.

Study 1

Digital images of 60 bile ducts obtained from PBC (30 ducts) and CVH (30 ducts) were randomly laid out, and numbered from 1 to 60. Observers were asked to identify the degree of bile duct injury as mild, moderate, or severe. Three other samples of injured bile ducts from PBC liver with mild, moderate, or severe injury were also included on the CD-ROM, as a reference to estimate the degree of bile duct injury (Fig. 2). Bile ducts with mild injury showed mild loss of polarity of the biliary epithelia, irregularity of the biliary lumen, and few lymphocytes between biliary epithelial cells. Bile ducts with severe injury showed a marked loss of polarity of the biliary epithelia, obscured biliary lumens, and many lymphocytes between biliary epithelial cells.

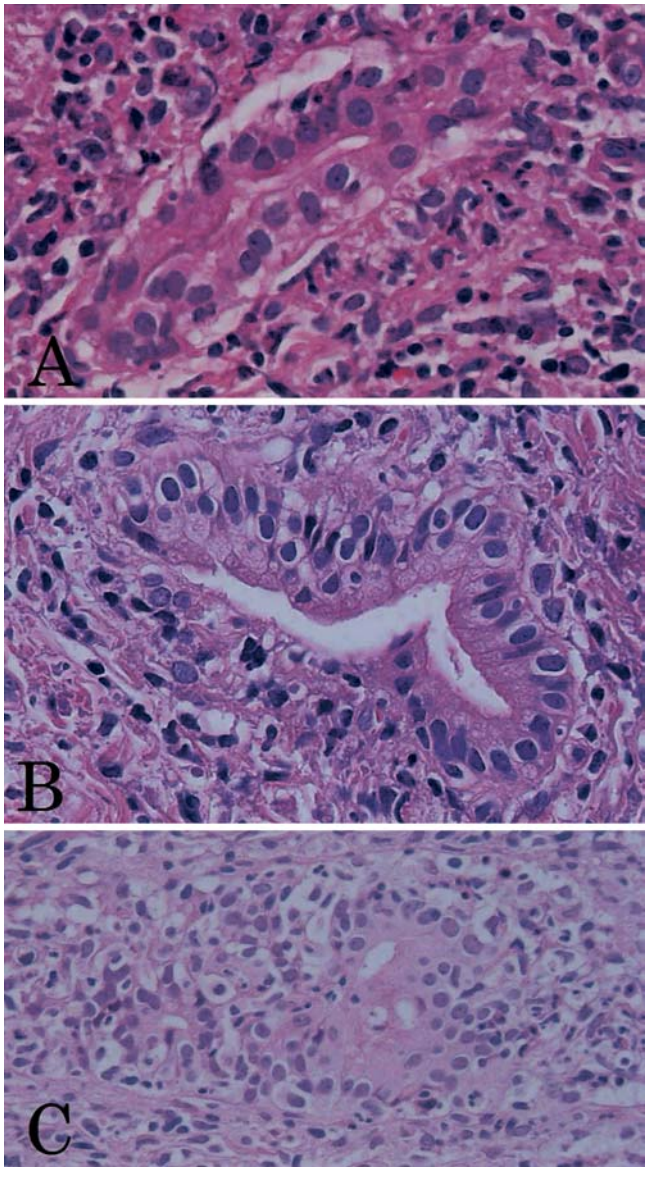

Fig. 2A–C. Samples of reference bile ducts for evaluating the degree of bile duct injury (**A**, mild injury; **B**, moderate injury; **C**, severe injury). These three bile ducts are from PBC. Digital images were recorded at a magnification of $\times 400$, and the images were trimmed squarely, using computer software

Moderate injury was defined as being between these entities.

Study 2

Each injured bile duct used in study 1 was categorized as either "PBC-associated" duct injury, "CVH-associated" duct injury, or "not determined".

Study 3

Thirty digital images of bile ducts from AIH were similarly recorded on CD-ROMs. Observers were asked to

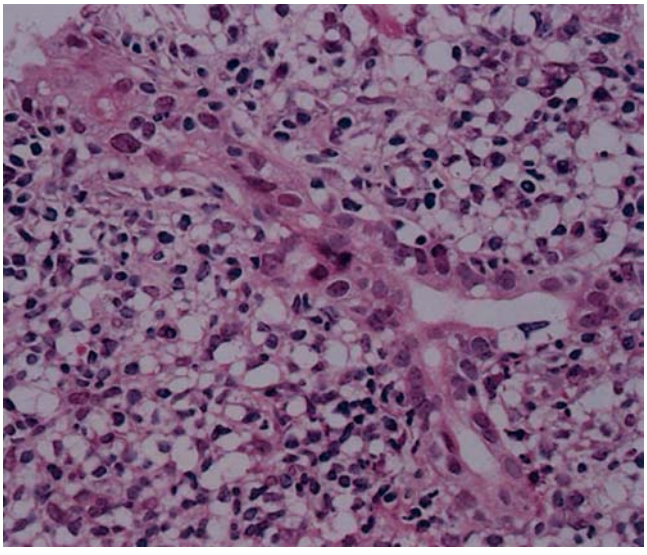

Fig. 3. Bile duct of AIH coincidentally evaluated as showing destructive cholangitis by ten observers. Irregularity or loss of bile duct lumen, loss of polarity of biliary epithelia, and lymphocyte infiltration between biliary epithelial cells are seen. Digital images were recorded at a magnification of $\times 400$, and the images were cut out squarely, using computer software

respond to two questions: (1) on the degree of bile duct injury; whether mild, moderate, or severe and (2) to categorize each injured bile duct as destructive cholangitis (resembling or equivalent to CNSDC), hepatitis-associated bile duct injury (resembling or equivalent to hepatitis-associated bile duct lesion), or not determined. Estimation of the degree of bile duct injury was based on the same samples as those used in study 1.

Data analysis

The answers to study 2 were subdivided into two groups: "PBC-associated bile duct injury", or "impossible to determine as PBC", including both "CVH-associated" and "not determined". Although "CVH-associated" and "not determined" bile duct injury may be different, these two groups were categorized together in one group based on the idea of the impossibility of diagnosing PBC only by the bile duct itself. The answers to question 2 in study 3 were also subdivided into two groups: "destructive cholangitis", or "nondestructive cholangitis", including "hepatitis-associated bile duct injury" and "not determined". Although "hepatitis-associated bile duct injury" and "not determined" may also be different, these two entities were categorized into one group, implying that neither of these two entities could be used to categorize bile ducts as having definitive destructive cholangitis of the PBC type.

Table 2. Interobserver agreement for evaluation of the degree of bile duct injury associated with primary biliary cirrhosis, chronic viral hepatitis, and autoimmune hepatitis

	Special hepatopathologists	Local hepatopathologists	General pathologists
Concordance rate	58.8%	64.1%	71.3%*
κ value	0.328	0.360	0.522*;**

* $P < 0.05$ vs special hepatopathologists; ** $P < 0.05$ vs local hepatopathologists

Table 3. Diagnostic rate and diagnostic specificity in diagnosis of primary biliary cirrhosis, based on bile duct injury alone, using 60 trimmed bile ducts from primary biliary cirrhosis and chronic viral hepatitis

	Special hepatopathologists	Local hepatopathologists	General pathologists
Mild injury (30 bile ducts)			
Diagnostic rate	50.0 ± 10.8%*	36.5 ± 8.5*;**	42.3 ± 6.7%*;**
Diagnostic specificity	0.74 ± 0.06	0.75 ± 0.10	0.85 ± 0.06
Moderate injury (23 bile ducts)			
Diagnostic rate	88.9 ± 2.2%	85.0 ± 6.3%	73.3 ± 10.5%
Diagnostic specificity	0.71 ± 0.07	0.68 ± 0.05	0.54 ± 0.09
Severe injury (7 bile ducts)			
Diagnostic rate	83.3 ± 10.5%	87.5 ± 12.5%	87.5 ± 12.5%
Diagnostic specificity	0.42 ± 0.15	0.50 ± 0.00	0.63 ± 0.13
Total (60 bile ducts)			
Diagnostic rate	71.6 ± 4.2%	65.8 ± 7.5%	60.8 ± 7.6%
Diagnostic specificity	0.72 ± 0.07	0.77 ± 0.04	0.75 ± 0.04

* $P < 0.05$ vs moderate injury; ** $P < 0.05$ vs severe injury

Table 4. Number and percentage of bile ducts in autoimmune hepatitis (30 bile ducts) evaluated as showing destructive cholangitis

	Special hepatopathologists	Local hepatopathologists	General pathologists
Number	6.5 (0–12)	10.0 (8–14)	11.8 (6–18)
Percentage	21.7%	33.3%	39.2%

The numbers of bile ducts are shown as averages (minimum–maximum)

Interobserver agreement was estimated regarding the degree of bile duct injury (90 bile ducts; PBC, CVH, and AIH). This interobserver agreement was calculated by the concordance rate (%) and the κ value. Interpretations of κ were as previously described,[14] i.e., less than 0.00, "poor agreement"; 0.00–0.20, "slight agreement"; 0.21–0.40, "fair agreement"; 0.41–0.60, "moderate agreement"; 0.61–0.80, "substantial agreement"; and 0.81–1.00, "almost perfect agreement".

The diagnostic rate and the diagnostic specificity in the diagnosis of PBC were estimated, based on randomly arranged pictures of bile ducts with PBC and CVH. The diagnostic rate was defined as the ratio of the number of cases correctly diagnosed as PBC / total number of PBC cases (30 cases). The diagnostic specificity was defined as the ratio of the number of cases correctly diagnosed as not PBC / total number of not-PBC cases (30 cases).

The Mann-Whitney *U*-test was employed, with a significance level of $P < 0.05$.

Results

Degree of bile duct injury

The interobserver agreement for evaluation of the degree of bile duct injury is shown in Table 2. The concordance rate among general pathologists (71.3%) was significantly higher compared to that among special hepatopathologists (58.8%). The κ value among general pathologists (0.522) was significantly higher than those

among special hepatopathologists (0.328) and local hepatopathologists (0.360).

Diagnosis of PBC

The diagnostic rate of PBC, in 60 trimmed bile ducts from PBC and CVH, for each observer group, is shown in Table 3. The diagnostic rate in these 60 bile ducts was slightly higher for the special hepatopathologists than the rates for the local hepatopathologists and general pathologists, although the difference was not significant. When the injured bile ducts of PBC were categorized into three groups based on the degree of bile duct injury, the diagnostic rate of PBC in mildly injured bile ducts was significantly lower than those of moderately or severely injured bile ducts. However the diagnostic specificity was higher as the degree of bile duct injury was milder. For the bile ducts with moderate injury, both the diagnostic rate and the diagnostic specificity for general pathologists were lower than those for the special and local hepatopathologists, although the differences were not statistically significant.

Evaluation of bile duct lesions encountered in AIH

The number and percentage of bile ducts in AIH that were evaluated as showing destructive cholangitis are shown in Table 4. Two of the special hepatopathologists evaluated all bile ducts as showing nondestructive cholangitis. The general pathologists evaluated 6–18 bile ducts as showing destructive cholangitis equivalent to CNSDC. The percentage of bile ducts showing destructive cholangitis evaluated by special hepatopathologists (21.7%) was lower than those evaluated by local hepatopathologists (33.3%) and general pathologists (39.2%), although there was no significant difference among these groups. The lower percentage for special hepatopathologists was influenced by the abovementioned two special hepatopathologists who evaluated all cases as nondestructive cholangitis. Seven of the 30 bile ducts were coincidentally evaluated as showing destructive cholangitis by more than half of the observers. Furthermore, two bile ducts were evaluated as showing destructive cholangitis by ten observers (Fig. 3).

Discussion

There have been no interobserver agreement studies on the histological estimation or evaluation of small bile duct injury in PBC, AIH, and CVH, so far. In this study, we analyzed differences in histological estimations of bile duct injury by 14 observers. It was found that the interobserver agreements for the degree of bile duct injury were slightly low (κ values: 0.328–0.522). This agreement was lower than our expectation before commitment to this study. Criteria for the degree of bile duct injury have not been proposed in the literature so far. Each observer may have estimated the degree based on their own diagnostic criteria, resulting in the low interobserver agreement. In addition, the interobserver agreement among general pathologists on the degree of bile duct injury was significantly better than those in the other two groups. The reasons for such data being obtained in this study remain only speculative. It seems possible that, because the hepatopathologists (special or local) have more experience, they may have established their own criteria for the bile duct injuries. This may have caused the low concordance rate for the degree of bile duct lesions in these two groups.

Forty to 83% (average, 66.9%) of PBC bile ducts from mixed samples of trimmed bile ducts from PBC and CVH were correctly diagnosed by observers. Diagnostic accuracy for PBC in severely injured bile ducts was higher (diagnostic rate, more than 80%) than that for the mildly injured bile ducts (50% or less). This result suggests that a diagnosis of PBC in severely injured bile ducts could easily be made based on trimmed bile duct alone. However, cases without such injury cannot be diagnosed by bile duct injury alone, and thus additional histological findings may be needed in such cases for the correct diagnosis of PBC. It is well known that PBC has several characteristic and diagnostic histological findings, in addition to cholangitis, such as granuloma formation, bile duct loss, eosinophilic infiltration, and chronic cholestatic changes (Mallory bodies in the periportal area, copper accumulation, feathery change).[1] In other words, PBC should not be excluded even when there is only mild bile duct injury, in which case other findings useful for the diagnosis of PBC should be searched for.

Interestingly, general pathologists tended to have diagnostic rates and diagnostic specificity for PBC similar to those of the special and local hepatopathologists (Table 3). However, for the bile ducts with moderate injury, these rates and specificities for general pathologists were slightly lower than those for the special and local hepatopathologists. That is, these findings suggested that, compared to general pathologists, hepatopathologists were superior in their evaluation of moderately injured bile ducts in PBC.

The AIH cases used in this study were originally diagnosed as pure AIH clinicopathologically, and none of the patients were suspected as having overlap syndrome. However, 9 bile ducts (average) of AIH (of a total of 30 bile ducts) were estimated as showing destructive cholangitis by all the observers, except for two hepatologists who evaluated all bile ducts as showing

nondestructive cholangitis. This result suggests that bile duct injury that is histologically indistinguishable from CNSDC of PBC could exist in AIH. This finding should be kept in mind, because the differential diagnosis of PBC from AIH is very important for their treatment.[15,16] The present study suggests that the differentiation of PBC from AIH or complications of PBC in AIH should not be based only on bile duct injury, and other findings of PBC (as mentioned above) or AIH (confluent necrosis, plasma cell infiltration, severe lobular hepatitis) should be comprehensively analyzed for correct diagnosis. However, because only cases of AIH with bile duct injury were selected for this analysis, the results of this study could not reflect the actual incidence of bile duct injury in AIH and CVH. In addition, some degree of bias could have emerged in the evaluation of bile duct injuries of AIH, because it was requested from each observer to estimate whether or not the bile duct injury of AIH was showing destructive cholangitis of the PBC type. However, the intention of this study was to obtain information on the occurrence of destructive bile duct injuries in AIH, and also to give us the message that severe destructive bile duct injury is not specific to PBC.

This study aimed at assessing interobserver agreement in diagnosing small bile duct lesions in PBC, CVH, and AIH. While some bile duct lesions in AIH resemble CNSDC of PBC, this does not suggest or imply that the bile duct injuries in PBC and AIH share a common pathogenetic process(es). That is, another approach must be used to evaluate the pathogenesis of individual duct lesions in PBC and AIH, and also in CVH.

This study had some limitations, because all the observers—Japanese pathologists or hepatologists—were educated and trained mostly only in Japan. Thus, it is difficult to conclude that the diagnostic rate and interobserver agreement obtained in this study would reflect findings elsewhere, because pathological estimation is usually influenced by diagnosticians' experiences and their training. Furthermore, in this study, there was no significant difference in the diagnosis of PBC among the special hepatopathologists, local hepatopathologists, and general pathologists. However, this result does not reflect the true diagnostic ability of these observers, because only bile duct images themselves were given to the observers in this study.

In conclusion, this study, examining only bile ducts histologically, revealed that the interobserver agreement in evaluating the degree of bile duct injury was slightly low (κ value, 0.328–0.522). The diagnosis of PBC in trimmed bile ducts alone from PBC and CVH was dependent on the degree of bile duct injury. Bile duct injury similar to CNSDC could be encountered in AIH. The histological diagnosis or evaluation of bile duct lesion(s) in individual patients should be done while taking into consideration histological features other than the degree of bile duct injury; also, of note, overestimation of the degree of bile duct injury is dangerous.

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