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Original Article

Pathological features of biopsy in autoimmune liver disease: a report of 109 cases

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Abstract: Autoimmune liver disease (AILD) is a group of hepatobiliary diseases and of autoimmune abnormalities, which includes autoimmune hepatitis (AIH, featured by hepatic parenchymal cell injury), primary biliary cirrhosis (PBC, featured by intrahepatic small bile duct injury and cholestasis) primary sclerosing cholangitis (PSC, characterized by major bile duct injury and cholestasis) and overlap syndrome (OS) that has characteristics of both AIH and PBC or PSC. In the early stage, clinical manifestations of each type of AILD is not obvious, and diagnosis is mainly based on the biochemistry, immunology, imaging and pathological features. Therefore, liver biopsy has important clinical value for the diagnosis of AILD and evaluation of the severity and prognosis. In this study, pathological characteristics of 109 cases of AILD patients were retrospectively analyzed.

Keywords: Pathological, autoimmune liver disease, autoimmune hepatitis, primary biliary cirrhosis, overlap syndrome

Introduction

Autoimmune liver disease (AILD) is a group of hepatobiliary diseases and of autoimmune abnormalities, according to the characteristics of clinical manifestations, biochemical, imaging and pathology, Its includes autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and overlap syndrome (OS) that has characteristics of both AIH and PBC or PSC.

Autoimmune hepatitis is an autoimmune mediated chronic progressive inflammatory liver disease, its clinical features are different degrees of elevated serumtransaminase, gamma-globulin, autoantibodies, histological, characterized by infiltration of lymphocytes and plasma cells of interface hepatitis, severe cases may progress rapidly to cirrhosis and liver failure.

Primary biliary cirrhosis mainly affects middle-aged women, the clinical manifestations were fatigue, anorexia, skin itching, hepatosplenomegaly. Pathological features include chronic, non suppurative inflammation of the interlobular bile ducts and destruction of granulomas, leading to progressive bile duct disappearance. Serum anti-mitochondrial antibodies (AMA) and type AMA-M2 positivity are important in diagnosis.

Primary sclerosing cholangitis is a major involvement of middle-aged men, with intrahepatic and extrahepatic biliary inflammation, fibrosis and occlusion of chronic progressive liver disease, bile duct stenosis interval to normal or dilated bile duct, the cholangiography showed the characteristic changes of beaded stenosis.

Patients and methods

Patients

Between September 2011 and December 2016, 109 AILD patients confirmed by liver biopsy in the Department of Gastroenterology of the Yan'an Hospital Affiliated to Kunming Medical University and the Second Affiliated Hospital of Kunming Medical University hospi-

Table 1. Autoimmune liver disease in 109 cases

Variable	Female: Male	Age	Cases (*n*)	%
AIH	22: 5	53.4±7.6	27	24.8%
PBC	46: 21	52.1±14.7	67	61.5%
PSC	3: 1	39.0±16.2	4	3.7%
AIH-PBC	8: 2	45.7±12.4	10	9.1%
AIH-PSC	1: 0	39	1	0.9%
Total	80: 29	50.8±13.4	109	100%

tal were recruited and retrospectively analyzed. All patients had negative hepatitis viral markers, no history of alcohol drinking or taking drugs known to have potential damage to the liver, and no other diseases related to liver damage. Informed consent was obtained from the subjects (or their guardians). This research was approved by the Ethics Committee of the Second affiliated hospital of kunming Medical University.

Methods

Observation items: (1) general status: including gender, age of the patients. (2) liver biopsy: rapid puncture of liver tissue guided by ultrasound, specimens under the microscope, 1.2-2.0 cm long, including at least 6 portal areas, conventional dehydration, paraffin embedded sections, HE staining, Masson staining and reticular fiber, HBsAg, HBcAg, HCV underwent immunohistochemical examination, by the Kunming Medical University Department of Pathology, the same standards of reading [1]. Informed consent was obtained from the subjects (or their guardians). This research was approved by the Ethics Committee of the Second affiliated hospital of kunming Medical University.

Diagnostic criteria: The diagnosis of AIH was according to the 1999 International Autoimmune Hepatitis Group (IAIHG) [2], which includes recommendation score diagnosis or descriptive diagnosis: scores on summation of more than 15 points to determine the diagnosis of AIH, 10-15 for possible AIH; PBC and PSC were diagnosed according to the 2000 American Association for the study of liver diseases (AASLD) guideline [3] and the 2002 the American Gastroenterological Association (ACG) guideline [4], respectively. Diagnosis of OS was according to the standards established by Lohse et al. [5].

Statistical methods: SPSS13.0 statistical software was applied for statistical analyses. Continuous data were expressed as mean ± standard deviation (SD); Categorical data were expressed as number and percentage. $P<0.05$ was considered statistically significant.

Results

Demographic characteristics

Women (80/109, 73.3%) were more common in patients with AILD, with an average age of 50.8±13.4 years old. AIH, PBC and AIH-PBC overlap syndrome in middle-aged women, accounted for (22/27, 81.4%), (46/67, 68.6%), and (8/10, 80%), respectively. The average ages of AIH, PBC, and AIH-PBC were 53.4±7.6, 52.1±14.7, and 45.7±12.4, respectively. The onset age of PSC is relatively young, with the average age of 39±16.2 years old. The age distribution is shown in **Table 1**.

Pathological features

All patients underwent liver biopsy, no bleeding and bile leakage and other complications, the specific microscopic characteristics were shown in **Table 2**.

AIH: The degrees of AIH ranged from G1S1 to G4S4. The main characteristics of the AIH included interface hepatitis (21/27, 77.7%), portal infiltration (22/27, 81.4%), and formation of lymphoid follicles (**Figure 1A**), severe inflammation (12/27, 44.4%), bridge necrosis (10/27, 37.1%). The age and sex distribution are shown in **Table 3**.

PBC: Features included granuloma formation and small bile duct loss in liver tissue (**Figure 1B**). 5 patients with early PBC had granuloma. Bile ducts in 42 PBC patients reduced or even disappeared (42/67, 62.6%). Of the 67 patients, early PBC (I, II) and III (late accounted for 28.3%, IV) accounted for 71.7% (**Table 4**).

PSC: In this group, bile ducts had reduced or disappeared with lymphocytic infiltration in 3 PSC patients. 1 cases of female patients had typical histological findings and the fibrous tissue around the bile duct was arranged in concentric circles (**Figure 1C**). There were 4 cases of patients in the late stage (**Table 5**).

OS: 10 cases of AIH-PBC overlap syndrome in histology showed both AIH and PBC dual char-

Table 2. Pathological results of the four groups

Variable	Cases (*n*)	Interface hepatitis	Peripheral hepatitis	Bridging necrosis	Lymphocytes infiltration	Granuloma	Bile duct hyperplasia	Small duct reduction	Pseudo-lobule
AIH	27	21	0	10	22	0	0	0	8
PBC	67	5	15	9	24	5	14	42	22
PSC	4	2	0	0	2	0	1	3	1
AIH-PBC	10	6	0	3	4	0	2	6	2

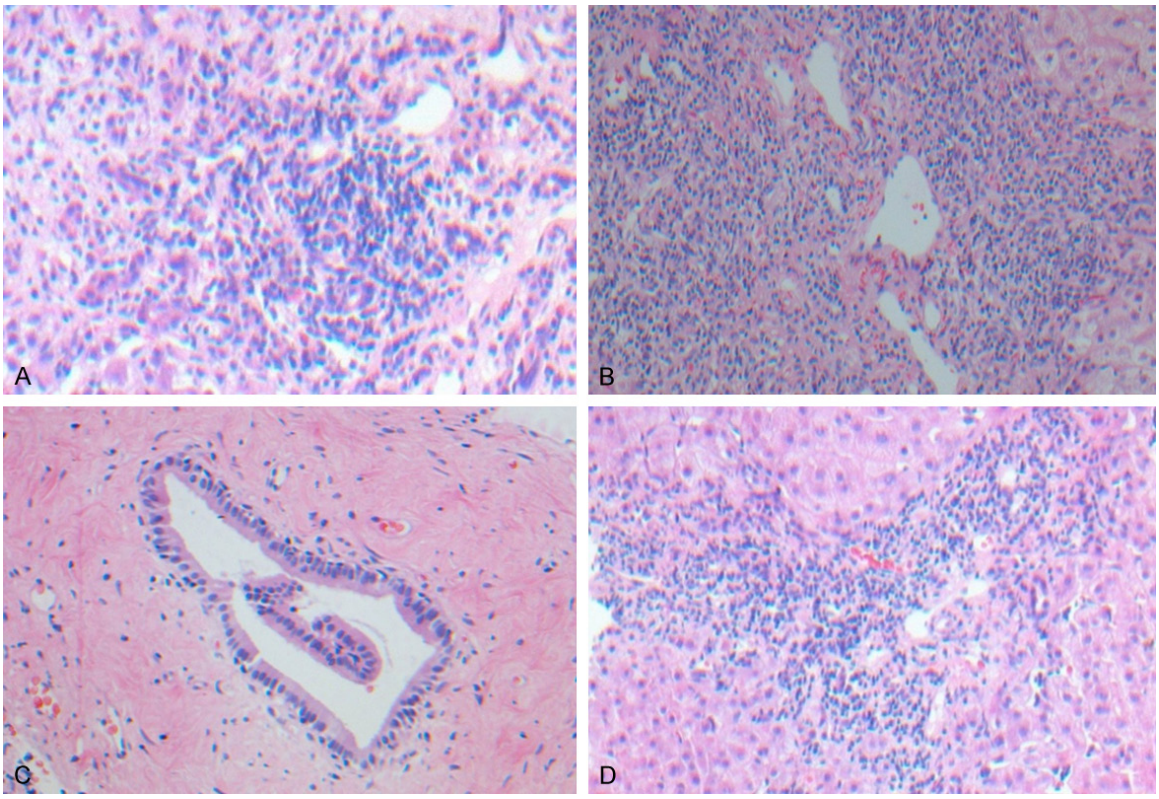

Figure 1. Pathological changes of autoimmune liver diseases (HE staining). A: AIH G3S3, a large number of lymphocytes infiltration, and the formation of lymphoid follicles (HE×400); B: PBC IV, small bile duct disappeared, pseudolobule (HE×400); C: The fibrous tissue is wrapped around the bile duct and arranged in concentric circles (HE×200); D: AIHG4S4-PBC IV, severe hepatitis with small bile duct disappearance and false lobule formation (HE×400).

Table 3. Autoimmune hepatitis in 27 cases

Stage	Cases (*n*)	Female: Male	Age					
G1S1	5	5:0	42	48	56	57	61	
G2S1	4	4:0	45	52	64	65		
G2S2	1	1:0	45					
G3S2	5	3:2	47	50$^{\Delta}$	58	58	60$^{\Delta}$	
G3S3	6	4:2	47	48	48$^{\Delta}$	50$^{\Delta}$	53	59
G3S4	2	2:0	46	46				
G4S4	4	3:1	44	64$^{\Delta}$	65	65		

$^{\Delta}$Male.

acteristics (**Tables 2** and **6**), among which 6 cases were seen with severe interface hepatitis, with small bile duct hyperplasia or disappearance (**Figure 1D**). It is worth noting that this study found AILD rare, with 1 cases of AIH-PSC overlap syndrome.

Discussion

AIH, PBC and PSC are considered to have the same autoimmune pathogenesis and similar pathological changes. In the early stage, inflammation located in the portal and periportal areas. The end-stage diseases occurred in cirrhosis. However, these lesions similar to the background, the difference of AIH, PBC and PSC showed obvious histopathological changes, suggesting that these diseases have a dif-

Table 4. Primary biliary cirrhosis in 67 cases

Stage	Cases (*n*)	Female: Male	Age					
			0-25	26-35	36-45	46-55	56-65	>65
PBC I	7	6:1	0	0	0	3	4 (1)	0
PBC II	12	9:3	0	1	1	3	3 (1)	4 (2)
PBC III	20	13:7	2 (1)	6 (1)	3 (1)	3 (1)	4 (2)	2 (1)
PBC IV	28	18:10	2	0	4 (2)	9 (4)	7 (2)	6 (2)

The number of male patients in brackets.

Table 5. Primary sclerosing cholangitis in 4 cases

Cases	Gender	Age	Stage
1	Male	27	PSC II
2	Female	32	PSC IV
3	Female	63	PSC III
4	Female	34	PSC IV

Table 6. Overlap syndrome in 11 cases

Cases	Gender	Age	Stage
1	Female	53	AIHG2S2-PBC I
2	Female	55	AIHG2S2-PBC II
3	Female	50	AIHG3S3-PBC III
4	Female	27	AIHG3S4-PBC IV
5	Male	33	AIHG3S3-PBC III
6	Female	56	AIHG2S2-PBC II
7	Female	57	AIHG3S3-PBC III
8	Female	59	AIHG3S3-PBC III
9	Female	31	AIHG3S4-PBC IV
10	Male	36	AIHG3S3-PBC III
11	Female	39	AIHG3S3-PSC III

ferent pathogenesis, which each has specific lesions (target autoimmune) [6].

The key pathological change of the AIH is interface hepatitis, namely piecemeal necrosis. The portal area and portal area inflammation is the main pathological manifestation of AIH, characterized by inflammation in the portal area, and liver damage caused by circle plate, tube around single or small clusters of chronic progressive liver cell necrosis the change from the angle of necrosis of liver cells called piecemeal necrosis and piecemeal necrosis due to associated with inflammatory cell infiltration in the liver lobular parenchyma and interstitial area at the junction, from another angle of inflammation also known as pathological interface hepatitis AIH [7]. Special point infiltration around the portal area and portal area inflammation the cell is mainly of lymphocytes and plasma cells, this piecemeal necrosis and lymphocytic piecemeal necrosis. PBC main lesions are destructive granulomatous lesions in cholangitis, interlobular bile duct basement membrane rupture. The cells into bile duct epithelial cells through the basement membrane rupture caused by bile duct, bile duct epithelial degeneration and necrosis, and cause epithelioid cell hyperplasia, granuloma formation, the morphological characteristics suggest that biliary epithelial immune attack is PBC [8].

From the early PBC to development of liver cirrhosis, histopathology was divided into 4 stages: stage I (stage gate tube), showed portal hepatitis, periportal enlargement, lymphocyte infiltration. II (tube around period), as the door around the tube of hepatitis, portal inflammation and portal to further aggravate hepatic cells around the portal area and the surrounding, with small bile duct hyperplasia, the formation of biliary piecemeal necrosis. Phase III (interval), showed the formation of fibrous septa between the portal areas, bile duct significantly reduced the number of cells around the portal area of liver, cholestasis feathery degeneration. IV (hardening phase) [9], the characteristic The biliary cirrhosis, destroy the normal structure of hepatic lobule and portal area between the fiber interval around the regenerative nodules of hepatocytes, bile duct formation pseudolobules, or even disappear, pathological characteristic of severe cholestasis [10, 11]. PSC with liver parenchyma changes is fibrous obstructive cholangitis, bile duct and bile duct showed inflammation, infiltration inflammatory cells were lymphocytes, proliferation of fibrous connective tissue like a fiber coil around peribiliary new onion dermatoid concentric structure of [12], an early manifestation of bile duct epithelium gradually progressed to epithelial defect and disappeared by fibrous scar tissue to replace PSC. From the early progress to cirrhosis, histologically divided into 4 stages, I and II lesions in the liver biopsy specimens and PBC to identify the late formation of fibrous septa, bile duct disappeared. Histopathological performance overlap syndrome, Must take into account the evidence

[13] hepatitis and pathological cholangitis components, only when there is a typical interface hepatitis, and clear necrotizing granulomatous cholangitis or fibrous obstructive cholangitis, only consider the true overlap syndrome, also must be combined with the laboratory detection of antibodies, in order to make the diagnosis of liver biopsy. Pathological examination is an important and reliable basis for the diagnosis of AILD [14], one can exclude occult hepatitis virus serum markers, some negative fatty liver disease and genetic metabolic liver disease, on the other hand can clear AILD in patients with histological staging, in order to guide the clinical diagnosis and treatment, especially the use and removal for the evaluation and classification of AIH immune inflammation inhibitor has important reference value.

The results of this study showed that histological staging in more than G2S2 In patients with advanced AIH number (18/27, 66.6%), for more performance for moderate and severe interface hepatitis with periportal lymphocytic infiltration, 10 cases of patients with severe illness, bridges appeared necrosis. The data of 4 cases of PBC patients without any clinical symptoms, only the pure GGT medical units increased to come to visit, AMA/AMA-M2 negative after liver biopsy for the diagnosis of PBC stage, but most of the PBC patients when the illness is serious, which (III, IV) accounting for 71.7%, of which 22 cases of patients with cirrhosis of the liver pathological feature of pseudo lobule, indicating that PBC has entered late, drug therapy, the prognosis is poor, need to consider liver transplantation [15]; 4 cases of PSC patients in 1 patients had characteristic of PSC proliferation of fibrous tissue surrounding the bile duct, the formation of onion skin concentric structure; and AIH-PBC overlap syndrome in 6 patients at the same time to see moderate and severe Interface hepatitis, with small bile duct hyperplasia or disappeared, suggesting that some patients also have liver cells and bile duct damage.

Conclusions

To sum up, AILD is increasing in China. For middle-aged female patients with abnormal liver function of unknown causes, after exclusion of other common causes of liver disease, AILD should be considered. For patients with early disease symptoms, atypical, or serum autoantibody negative, liver biopsy for further diagnosis and histological staging is imperative. Early diagnosis and timely treatment for these patients can be established.

Disclosure of conflict of interest

None.

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