Relationship between clinical and pathologic findings in patients with chronic liver diseases

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INTRODUCTION

Liver fibrosis is a common sequel to diverse liver injuries. It is characterized by an accumulation of interstitial collagens and other matrix components[1-4]. Chronic liver diseases usually develop into liver cirrhosis through the phase of liver fibrosis[5-8]. In recent years, researchers have been making efforts to study the noninvasive diagnostic methods of liver fibrosis[9-15]. Through a multi-center study, we carried out a comparative analysis of 200 patients with chronic liver diseases by comparing their clinical manifestations, serum biochemical markers with histopathological findings in liver biopsy, in order to appraise the relationship between clinical findings of patients with chronic liver diseases and the grading and staging of liver tissues, and to provide clues and basis for the noninvasive diagnosis of liver fibrosis.

MATERIALS AND METHODS

Patients recruitment

The study was organized and carried out by Shanghai Cooperative Group of Hepatic Fibrosis Project. The Cooperative Group was led by Renji Hospital and Changzheng Hospital in Shanghai. Cases provided by the Cooperative Group were as follows: 37 from Changzheng Hospital, 36 from Renji hospital, 30 from Putuo District Central Hospital, 22 from Shanghai Hepatic Disease Center of Nanjing Military Command, 20 from Changzheng Hospital, 14 from Zhongshan Hospital, 11 from Huashan Hospital, 9 from Shibei Hospital, 8 from Shanghai No. 6 People’s Hospital, 6 from Shanghai Infectious Diseases Hospital, 3 from Ruijin Hospital, 3 from Shanghai No. 9 People’s Hospital, 1 from Shanghai No. 1 People’s Hospital. A total of 200 patients between July and October 1999 were recruited, including 156 male and 44 female patients. The average age of the patients was 34 years (range 15-60 years).

Histological examination

Within 1 week after admission, all the patients received liver puncture biopsy under the guidance of B ultrasound with the 14G quick-cut needle (8-light Company, Japan) or Menghini needle. The length of liver specimens was just 1 cm or longer. The samples were fixed with 10 % formaldehyde, embedded in paraffin and sliced, stained with hematoxylin-eosin, reticular fibers and collagenous fibers. According to the prevention and
treatment program for virus hepatitis set up in 1995[16], all the patients were graded and staged for liver fibrosis and inflammatory activity. Three pathologists read the slides, respectively. The results were statistically analyzed with Kappa test. It was revealed that the consistency of the grading and staging by the pathologists was excellent. All the pathologic diagnoses of liver biopsy were performed by Department of Pathology, Medical College of Fudan University.

Clinical data

General data The general data included age (-25, 25-35, 35-), course of disease (from the time when hepatic symptoms or abnormal laboratory parameters appeared for the first time to the present study) and gender.

Degree of hepatitis The degree of hepatitis was clinically evaluated according to the criteria recommended at the meeting of prevention and treatment of viral hepatitis held in 1995. Clinical symptoms According to the severity of clinical symptoms such as fatigue, inappetence, swelling, nausea, ache in hepatic region and gingival bleeding, it was scored as 0: no symptom; 1:with one kind of mild symptoms; 2: with one kind of symptoms between mild and severe; 3: with one kind of serious symptoms. It was further divided into 3 grades according to the totaled score: mild: 0-1, moderate: 2-3, severe: 4+. Physical signs According to the degree of hepatomegaly and splenomegaly, it was scored as 0: no hyperplasia (maximal oblique diameter of the right liver <14 cm, thickness of the spleen <4.0 cm); 1: with hepatomegaly (maximal oblique diameter of the right liver ≥14 cm); 1.5: with mild splenomegaly (thickness of the spleen was between 4-6 cm); 2: with splenomegaly above moderate degree (thickness of the spleen ≥6.0 cm). It was further divided into 4 grades according to the totaled score: 0: no hyperplasia, 1:hepatomegaly, 1.5: mild splenomegaly, and 2.5: splenomegaly above moderate degree or both splenomegaly and hepatomegaly.

Laboratory parameters

Routine blood test Red blood cells (RBC), white blood cells (WBC) and platelets (PLT) were counted.

Biochemical blood test Total serum bilirubin, AST, ALT, AST/ALT, GGT, albumin (A), albumin (A)/globulin (G), γ-globulin, prothrombin time (PT), apoprotein A1(ApoA1), α2-macroglobulin and α-fetoprotein(AFP) were detected. Among them, PT, GGT and Apo-A1 were integrated as PGA index. PGA and α2-macroglobulin were integrated as PGAA index.

Serum viral markers HBsAg, HBeAg, anti-HBe, anti-HBc, HBV-DNA, anti-HCV and HCV-RNA were detected.

Serum fibrosis parameters Hyaluronic acid (HA), lamolin (LN), N-terminal procollagen III(PIII NP), 7S collagen IV(7S-IV) were included.

Statistical analysis

Analysis of variance was carried out for all the data with SAS software. $P<0.05$ was considered statistically significant.

RESULTS

Relationship between general data and pathological grading and staging of liver tissues

It was revealed that there was a significant difference in inflammatory activity and fibrosis among different age groups (-25, 25-35, 35-) ($P<0.05$). With the increase of age, the degree of fibrosis became more severe. However, there was no significant difference in inflammatory activity and fibrosis between different courses of disease (-1 year, 1-5 years, 5-years) and sexes ($P>0.05$).

Relationship between clinical manifestations and pathological staging of liver fibrosis

The statistical results indicated that there was a significant difference between the severity of hepatitis and inflammatory grading, and fibrosis staging of liver tissues ($P<0.01$) (Table 1).

The symptom accumulation score at different stages of liver fibrosis was significantly different ($P<0.05$). With the increase of score, liver fibrosis tended to be more serious. However, there was no difference between symptom score and inflammatory grading. Statistical analysis of single symptom indicated that only nausea and gingival bleeding had a significant difference at different stages of liver fibrosis ($P<0.05$ and $P<0.01$, respectively).

Among different grades of inflammatory grading and fibrosis staging, the score of physical signs differed significantly ($P<0.05$), with the increase of score, inflammatory and fibrosis became more serious.

When symptom score and physical scores were combined for a further analysis, all the subjects were divided into 6 groups (Table 1). There were correlations between the inflammatory activity and fibrosis staging, and the differences among different groups were significant ($P<0.01$).

Table 1. Relationship between clinical manifestations and pathological grading and staging of liver tissues

| Groups | Symptom score+physical signs | n | Inflammatory grading (G) (%) | Fibrosis staging (s) (%) |
|--------|-----------------------------|---|----------------------------|------------------------|
|        |                             |   | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| 1      | 0-1+no hepatomegaly and splenomegaly | 15 | 46.7 | 40 | 13.3 | 0 | 33.3 | 26.7 | 40 | 0 | 0 |
| 2      | 0-1+hepatomegaly and splenomegaly | 14 | 28.6 | 28.6 | 28.6 | 14.3 | 7.1 | 35.7 | 28.6 | 14.3 |
| 3      | 3+no hepatomegaly and splenomegaly | 28 | 42.9 | 53.6 | 3.5 | 0 | 14.3 | 50 | 35.7 | 0 | 0 |
| 4      | 2-3+hepatomegaly and splenomegaly | 42 | 30.9 | 26.2 | 28.5 | 16.7 | 9.5 | 23.8 | 40.5 | 16.7 | 9.5 |
| 5      | 4+no hepatomegaly and splenomegaly | 32 | 43.7 | 25 | 15.6 | 15.6 | 12.5 | 34.3 | 25 | 15.6 | 12.5 |
| 6      | 4+hepatomegaly and splenomegaly | 69 | 23.3 | 21.7 | 34.8 | 15.9 | 2.9 | 29 | 29 | 15.9 | 23.2 |

P<0.01 P<0.01
Relationship between PGA, PGAA index and pathological staging and grading

PGA score had a relationship with inflammation and fibrosis ($P<0.01$, $P<0.05$ respectively). Its sensitivity and accuracy for the diagnosis of liver fibrosis were 70.33 % and 67.33 %, respectively, both of which were higher than those for early liver cirrhosis (50.00 % and 57.14 %, respectively). PGAA also correlated with inflammation and fibrosis ($P<0.05$), the sensitivity and accuracy for the diagnosis of liver fibrosis were 63.74 % and 63.37 %, respectively, both of which were higher than those for early liver cirrhosis (33.33 % and 61.64 %, respectively).

Relationship between serum parameters of liver fibrosis and pathological grading and staging

With discriminatory analysis method, we evaluated the significance of assaying single or combined serum parameters of liver fibrosis, in the diagnosis of liver fibrosis and cirrhosis (Tables 3 and 4).

Relationship between viral markers and pathological staging and grading

The statistical results revealed that there was no relationship between viral replication parameters and degrees of inflammation and fibrosis.

DISCUSSION

This study suggested that age was correlated with inflammatory activity, but the course of disease did not. Maybe it is because most of the patients were unaware of the disease, but the course of disease was always calculated from the time when symptoms appeared or people saw a doctor. It could not reflect the course accurately. So it was difficult to discover the relationship between fibrosis severity and the course of the disease.

With the integral method, we scored the severity of symptoms quantitatively, classified the total score, which could reflect the symptom severity comprehensively. The results indicated that there was no correlation between symptom score and the course of disease.

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Table 2  Relationship between biochemical parameters and inflammatory grading and fibrosis staging

| Parameters | Inflammatory (G) (%) | Fibrosis staging (s) (%) |
|------------|----------------------|-------------------------|
|            | 1-2  | 1-3  | 1-4  | 2-3  | 2-4  | 3-4  | 0-1  | 0-2  | 0-3  | 0-4  | 1-2  | 1-3  | 1-4  | 2-3  | 2-4  | 3-4  |
| RBC        | b    | b    | b    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    |
| PLT        | b    | b    | b    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    |
| AST        | b    | b    | a    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| ALT        | a    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| GGT        | a    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| A/G        | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| HA         | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| LN         | a    | b    | a    | b    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    |
| 7S-IV      | a    | b    | a    | b    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    | a    |
| PIIIINP    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| AFP        | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |
| PT         | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    | b    |

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$^aP < 0.05, \hspace{0.5cm} ^bP < 0.01.$

Table 3  Serologic parameters for diagnosing liver fibrosis and cirrhosis

| Parameters | Fibrosis (S0/S1-4) | Cirrhosis (S1-3/ S4) |
|------------|-------------------|---------------------|
|            | Specificity(%)    | Sensitivity(%)      | Accuracy(%)   | Specificity(%)    | Sensitivity(%)      | Accuracy(%)   |
| HA         | 94.44             | 38.26               | 43.50         | 90.0              | 60.0                | 85.71         |
| PIIIINP    | 16.67             | 77.71               | 72.00         | 78.0              | 24.0                | 70.28         |
| LN         | 55.26             | 50.29               | 50.10         | 54.0              | 52.0                | 53.71         |
| 7S-IV      | 50.22             | 24.67               | 51.00         | 93.29             | 24.0                | 89.08         |

Table 4  Serologic parameters for diagnosing liver fibrosis and cirrhosis

| Parameters | Fibrosis (S0/S1-4) | Cirrhosis (S1-3/ S4) |
|------------|-------------------|---------------------|
|            | Specificity(%)    | Sensitivity(%)      | Accuracy(%)   | Specificity(%)    | Sensitivity(%)      | Accuracy(%)   |
| HA+7S-IV   | 88.89             | 37.93               | 42.50         | 89.93             | 60.0                | 85.63         |
| HA+PIIIINP | 88.89             | 42.86               | 47.10         | 90.0              | 60.0                | 85.71         |
| HA+7S-IV+  | 88.89             | 47.13               | 51.04         | 89.93             | 64.0                | 86.21         |
| PIIIINP+LN | 92.86             | 38.28               | 43.67         | 90.27             | 60.0                | 86.72         |
| HA+TIMP   | 60.00             | 60.44               | 60.40         | 89.41             | 66.67               | 87.91         |
| PG +HA    | 70.00             | 62.64               | 63.67         | 89.41             | 66.67               | 87.91         |
| PGAA +HA  | 61.12             | 50.22               | 50.31         | 90.59             | 33.33               | 86.80         |
| PGAA +7S-IV | 60.00           | 48.22               | 50.67         | 92.94             | 33.33               | 89.00         |
and inflammatory activity (P<0.05), but the score correlated with fibrosis stage significantly (P=0.0106). With the symptoms becoming more prominent, fibrosis became more serious. At the same time, it was found that the score of physical signs had a strong relationship with inflammatory activity and fibrosis severity (P<0.05). The higher the physical sign score was, the more serious the inflammatory activity and fibrosis were. When the difference became more significant, the symptoms and signs were combined (P<0.01).

This study indicated that at different fibrosis stage and inflammatory grade of liver tissues, the serum level of HA differed remarkably (P<0.01), which could serve as a sensitive and accurate parameter to identify the severity of hepatic inflammation and fibrosis[17-20]. In addition, HA was a specific and accurate parameter for the diagnosis of early liver cirrhosis, the specificity and accuracy were 90 % and 85 %, respectively. It was also found that PIIINP differed at the different inflammatory grades significantly (P<0.01), but not significantly at different fibrosis stages (P>0.05), indicating that its correlation with inflammatory severity was closer than that with fibrosis. Thus it might be of significance in determining the inflammatory severity.

One conclusion that differs from others is that this study did not agree with the significance of LN in the diagnosis of liver fibrosis. It has been claimed that the diagnostic efficiency would increase when HA was assayed in combination with other parameters, yet it needs to be proved[21-24].

Based on the relationship between a single biochemical parameter and inflammation and fibrosis, we found that PLT, RBC and AST were important in identifying inflammatory severity rather than fibrosis. They differed significantly at grades 1, 2, 3 and 4, so they could help estimate the severity of inflammation. With the inflammation becoming serious, RBC and PLT tended to decrease. Both A and A/G ratio correlated with inflammation and fibrosis, and could be used to identify the severity. Additionally, our study proved that the level of AFP differed significantly at different inflammatory grades and fibrosis stages (P<0.01), indicating that it correlated with inflammation and fibrosis closely, and could be used as an adjuvant parameter[29-32].

PGA (PT, GGT, and ApoA1) and PGAA (PGA+α2-macroglobulin) index were mainly used as liver function indicators put forward in the early 1990’s by some experts to reflect the liver function of patients with alcoholic liver disease, and to screen or diagnose liver cirrhosis[33-38].

In recent years, researchers in China have probed into applying PGA index or combining it with other serum parameters to the diagnosis of liver cirrhosis. To some extent, the results of our study are in accordance with the conclusion that both PGAA and PGA correlated with inflammation and fibrosis significantly. However, when the foreign criteria were used, the score of ApoA1 in most normal samples were 4, which were too high, resulting in the increase of total PGA and PGAA scores. Therefore, we considered it abnormal when PGA score was above 6. This difference might be due to the following reasons. First, there was an ethnic difference in the normal range of ApoA1, so it is necessary to set up PGA and PGAA criteria applicable in China. Second, the two parameters were mainly used in alcoholic liver diseases, but most of the patients in our study were viral hepatitis[13-15,17,33,36,39,40].

Our study indicates that, viral replication parameters such as HBsAg and HBV DNA have no correlation with the severity of inflammation and fibrosis. We compared the inflammatory and fibrotic severity in patients with positive markers of hepatitis B only (141 cases) and in those with positive markers of both hepatitis B and C (10 cases), but no statistical difference was found between them. However, as the patients suffering from co-infection of hepatitis B and C were very few in the study, the conclusion needs to be verified by larger sample studies.

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