Original Article

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Chronic Hepatitis C in Chronic Renal Failure Patients at Siriraj Hospital

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ABSTRACT

Background: There are few information related to the natural history of HCV infection in CRF patients. Dialysis patients generally have higher morbidity and mortality rates than those of the general population, due to their age and comorbid conditions. Thus, the long term consequences of HCV infection in these groups of patients are difficult to establish.

Objective: The study aims to assess the clinical, biological, virological and histological features in patients with CRF attending Siriraj Hospital, and to identify the predictors associated with liver fibrosis.

Patients and Methods: The medical files of all chronic hepatitis C with CRF who underwent liver biopsy at our unit between 1995 and 2004 were retrospectively reviewed. Demographic characteristics , risk factors for HCV infection, alcohol history, duration from the onset of HCV and CRF up to the time of liver biopsy and history of previous renal transplantation (RT). Patient were then categorized into 2 groups : group 1; no fibrosis and group 2; fibrosis score ≥1. Percutaneous liver biopsy was performed and used the grading and staging system scored quantitatively by Knodell's scoring system. The baseline characteristics of all patients were reported as median [min, max], median ± SD and proportions. For all analyses, p values of ≤0.05 were considered to be statistically significant.

Results: The mean age of 15 CHC with CRF patients was 43.6 years. The male:female ratio was 9:5. Seven percent of patients had history of alcohol abuse. The risk factors of CHC infection were identified in 11 of 15 patients (7 blood transfusion, 3 tattooing, 1 injection drug use), and the mean time from the possible exposure to HCV to liver biopsy was 10.5 years. Comparison between the group without liver fibrosis [10/15; (66%)] and the group with fibrosis [5/15; (34%)], revealed no significant differences between both groups with regard to age, gender, history of alcohol drinking, duration from the possible exposure to HCV to liver biopsy and the duration from the diagnosis of CRF to liver biopsy. Patients with liver fibrosis had longer duration from possible exposure to HCV than patients without fibrosis.

Conclusion: In our study, there was no significant relationship between fibrosis in the liver biopsy specimens and other parameters, except for the serum albumin and the platelet levels.

Key words : chronic hepatitis C, chronic renal failure, fibrosis

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BACKGROUND

Chronic hepatitis C (CHC) infection is common in patients with chronic renal failure (CRF). The prevalence of CHC in CRF varies from 10-60% in various geographic areas.[1,2] In Thailand, Luengrojanakul, P et al. reported that 20% of all hemodialysis or renal transplantation (RT) patients, were positive for HCV RNA. In contrast, none of the 55 patients who were on peritoneal dialysis was positive.[3]

There are few information related to the natural history of HCV infection in CRF patients. Dialysis patients generally have higher morbidity and mortality rates than those of the general population, due to their age and comorbid conditions. Thus, the long term consequences of HCV infection in these groups of patients are difficult to establish. However, data from USRDS and RLDT have shown that the death rate of dialysis patients with cirrhosis was 35% higher than those without cirrhosis.

An important study on the mortality of HCV in dialysis patients was reported in 2000 by Nakayama, et al who prospectively studied 1,470 chronic HD patients from 16 centers in Japan over a 6 year follow-up period[4]. Anti-HCV seropositivity was notably an independent risk factor for death (RR, 1.6; 95% CI 1.2-2.0, $p \leq 0.001$). Hepatocellular carcinoma accounted for 5.5% of all deaths in the anti-HCV-positive group compared with none in the anti-HCV-negative group (5.5% vs. 0%, $p \leq 0.001$). Cirrhosis was documented in 8.8% and 0.4% of patients who died in the anti-HCV-positive and -negative groups respectively ($p \leq 0.001$). Deaths occurring in HCV-infected patients on HD are clearly related to liver cirrhosis.

Mathurin *et al*., retrospectively studied 834 RT recipients over a 10-years follow-up period[5]. There was no survival differences seen at 5 years follow-up period. However, at 10 years the patient survival and the graft-survival rates in HCV-infected patients were significantly lower than those seen in uninfected matched RT controls, $65 \pm 5\%$ versus $85 \pm 3\%$ for patient survival ($p \leq 0.001$), and $49 \pm 5\%$ versus $69 \pm 4\%$ for graft survival ($p \leq 0.01$), respectively. Similar results were recently reported in the second decade compared with noninfected controls.[6,7]

The evaluation of HCV severity is complicated by the observation that aminotransferase levels are typically lower in dialysis patients than in the nonuremic population[8-11]. The authors concluded that there was no correlation between aminotransferase level, viral load and liver histology in ESRD patients. So liver biopsy remains the gold standard to define the grade and the stage of liver disease in these patients, especially in RT candidates.[12]

Some authorities offer antiviral therapy to those patients on dialysis who are otherwise suitable for RT. However, the decision for therapy in these patients should be based on histological severity of the liver disease, comorbidities, and tolerance of side effects.[13]

Objective

The study aims to assess the clinical, biological, virological and histological features in patients with CRF attending Siriraj Hospital, and to identify the predictors associated with liver fibrosis.

PATIENTS AND METHODS

Patients

The medical files of all chronic hepatitis C with CRF who underwent liver biopsy at our unit between 1995 and 2004 were retrospectively reviewed. Patient were then categorized into 2 groups in accordance with the liver histopathologic features : group 1; no fibrosis and group 2; fibrosis score $p \geq 1$.

Data Collection

Data were collected from the retrospective chart review. Demographic characteristics included age, sex, race, risk factors for HCV infection (injection drug use, tattooing, blood transfusion), alcohol history, duration from the onset of HCV and CRF up to the time of liver biopsy and history of previous renal transplantation (RT). Laboratory parameters included serum bilirubin, serum alanine transferase (ALT), serum aspatate transferase (AST), alkaline phosphates (ALP), gamma-glutamyl transpeptidase (GGT), albumin , platelet count and prothrombin time.

Virologic Parameters

Quantitative HCV-RNA assay and HCV genotype.

Liver Histology

Percutaneous liver biopsy was performed in all patients. Grading and staging were scored quantitatively using the histological activity index (HAI) Knodell's scoring system. All specimens were evalu-

ated using the first three components of the Knodell's scoring system for activity: periportal ± bridging necrosis (range of score 0-10), intralobular degeneration and focal necrosis (score 0-4), portal inflammation (score 0-4).

The scoring system for staging fibrosis included: no fibrosis = 0; periportal fibrous expansion (mild) without septa formation = 1; portal portal septa (>1 septum) with intact architecture (moderate) = 2; portal-central septa (>1 septum) with architectural distortion (severe) = 3; and cirrhosis = 4.

HAI for numerical scoring of liver biopsy specimens[a] (Table 1)

Definition

1. The estimated duration of HCV infection was defined as the time interval from the first risk factor exposure (injection drug use, tattooing, blood transfusion and unknown cause) to the time of liver biopsy.

2. Renal transplantation patients were divided into patients with functional allograft and patients with a failed transplantation who were put back to dialysis at the time of this study.

Statistical Analysis

The baseline characteristics of all patients were reported as median [min, max], median ± SD and proportions. The clinical, biochemical, and virological parameters were analyzed to determine any correlation with the histopathological features, using univariate analyses. For univariate analysis, chi-square test or fisher exact test was used for categorical variables while Mann-Whitney U test was used for quantitative variables. For all analyses, p values of ≤0.05 were considered to be statistically significant.

Table 1

I. Periportal ± bridging necrosis	Score	II. Intralobular degeneration and focal necrosis[b]	Score	III. Portal inflammation	Score	IV. Fibrosis	Score
A. None	0	A. None	0	A. No portal inflammation	0	A. No fibrosis	0
B. Mild piecemeal necrosis	1	B. Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in .1/3 of lobules or nodules)	1	B. Mild (sprinkling of inflammatory cells in ,1/3 of portal tracts)	1	B. Fibrous portal expansion	1
C. Moderate piecemeal necrosis (involves less than 50% of the circumference of most portal tracts)	3	C. Moderate (involvement of 1/3-2/3 of lobules or nodules)	3	C. Moderate (increased inflammatory cells in 1/3-2/3 of portal tracts)	3	C. Bridging fibrosis (portal- portal or portal-central linkage)	3
D. Marked piecemeal necrosis (involves more than 50% of the circumference of most portal tracts)	4	D. Marked (involvement of .2/3 of lobules or nodules)	4	D. Marked (dense packing of inflammatory cells in .2/3 of portal tracts)	4	D. Cirrhosis	4
E. Moderate piecemeal necrosis plus bridging necrosis[d]	5						
F. Marked piecemeal necrosis plus bridging necrosis[d]							
G. Multilobular necrosis[e]	10						

[a] HAI score is the combined scores for necrosis, inflammation, and fibrosis.
[b] Degeneration: acidophilic bodies, ballooning; focal necrosis: scattered foci of hepatocellular necrosis.
[c] Loss of normal hepatic lobular architecture with fibrous septae separating and surrounding nodules.
[d] Bridging is defined as $2 bridges in the liver biopsy specimen; no distinction is made between portal-portal and portal-central linkage
[e] Two or more contiguous lobules with panlobular necrosis.

RESULTS

Demographic Data

The mean age of 15 CHC with CRF patients was 43.6 years. The male:female ratio was 9:5. Seven percent of patients had history of alcohol abuse. The risk factors of CHC infection were identified in 11 of 15 patients (7 blood transfusion, 3 tattooing, 1 injection drug use), and the mean time from the possible exposure to HCV to liver biopsy was 10.5 years. The causes of CRF were identified in 7of 15 patients (1 chronic tubulointerstitial nephritis, 3 IgA nephropathy and 3 chronic glomerulonephritis) and the mean time from the diagnosis of CRF to liver biopsy was 8.1 years. In this study, 5 of 15 patients (34%) had history of RT, 1 with functional allograft and 4 with a failed transplantation back on dialysis at the time of study. The mean duration from failed transplantation to liver biopsy was 2.8 years (1-6 years) before liver biopsy.

Comparison between the group without liver fibrosis [10/15; (66%)] and the group with fibrosis [5/15; (34%)], revealed no significant differences between both groups with regard to age, gender, history of alcohol drinking, duration from the possible exposure to HCV to liver biopsy and the duration from the diagnosis of CRF to liver biopsy. Patients with liver fibrosis had longer duration from possible exposure to HCV than patients without fibrosis.

Laboratory Parameters

The mean AST and ALT values were 36 and 48 mg/dl respectively. Eight of 12 patients (66.6%) had normal AST, while 4 of 12 (33.3%) had normal ALT measurements. Comparing the two patient groups, se-

Table 2

	Fibrosis	F0	F(1)	Total	p-value
Gender	M/F	5/5	4/1	9/5	0.580
Age	Mean ± SD	44 ± 11	43 ± 3	44 ± 9	0.859
	Median (range)	43 (30-66)	44 (40-47)	43 (30-66)	
Alcohol	Y /N	1/9	0/5	1/14	1.000
History of RT	Y /N	2/8	3/2	5/10	0.251
Duration from possible	Mean ± SD	8.6 ± 7.1	14.4 ± 11.2	10.5 ± 8.7	0.325
exposure HCV to biopsy	Median (range)	7.5 (1-23)	13 (1-30)	10 (1-30)	
Duration from diagnosis	Mean ± SD	9.3 ± 7.3	5.6 ± 3.4	8.1 ± 6.4	0.440
CRF to biopsy	Median (range)	8.5 (1-25)	5.0 (2-10)	7.0 (1-25)	
AST	Mean ± SD	34 ± 13	41 ± 46	36 ± 26	0.710
	Median (range)	35 (17-55)	25 (7-109)	33 (7-109)	
ALT	Mean ± SD	45 ± 25	55 ± 41	48 ± 29	1.000
	Median (range)	56 (8-74)	49 (11-110)	54 (8-110)	
ALP	Mean ± SD	117 ± 39	167 ± 135	131 ± 72	0.630
	Median (range)	107 (71-189)	162 (35-304)	115 (35-304)	
GGT	Mean ± SD	107 ± 72	103 ± 97	105 ± 76	1.000
	Median (range)	94 (37-205)	52(41-215)	76 (37-215)	
ALB	Mean ± SD	3.98 ± 0.49	4.45 ± 0.13	4.12 ± 0.46	0.050
	Median (range)	4.100 (3.0-4.7)	4.450 (4.3-4.6)	4.300 (3.0-4.7)	
PT	Mean ± SD	11.44 ± 1.14	12.82 ± 1.48	11.90 ± 1.38	0.214
	Median (range)	11.10 (10.3-13.2)	12.95 (10.9-14.5)	11.55 (10.3-14.5)	
Platelet	Mean ± SD	$222 \times 10^9 \pm 49 \times 10^9$	$174 \times 10^9 \pm 19 \times 10^9$	$207 \times 10^9 \pm 47 \times 10^9$	0.050
	Median (range)	216×10^9 (155×10^9-289×10^9)	176×10^9 (151×10^9-192×10^9)	193×10^9 (151×10^9-289×10^9)	
Viral load	Mean ± SD	$46.12 \times 10^5 \pm 76.23 \times 10^5$	$24.88 \times 10^5 \pm 24.38 \times 10^5$	$37.62 \times 10^5 \pm 59.56 \times 10^5$	0.914
	Median (range)	16.08×10^5 (600-198×10^5)	21.55×10^5 (2290-56.40×10^5)	20.45×10^5 (600-198×10^5)	
Necroinflammation	Mean ± SD	2.2 ± 2.4	5.8 ± 3.0	3.4 ± 3.1	0.031
score (0-14)	Median(range)	1.5 (0-7)	5.0 (3-9)	3.0 (0-9)	

Table 3

CHC with ESRD patients		CHC with ESRD patients	
Periportal ± bridging necrosis score		**Portal inflammation score**	
0	6/15 (40%)	0	4/15 (27%)
1	6/15 (40%)	1	5/15 (33%)
3	3/15 (20%)	3	6/15 (40%)
4, 5, 10	0/15	4	0/15
Intralobular degeneration and focal necrosis score		**Fibrosis score**	
0	6/15 (40%)	0	10/15 (66%)
1	7/15 (47%)	1	4/15 (26%)
3	2/15 (13%)	3	1/15 (8%)
4	0/15	4	0/15

rum AST, ALT and ALP levels were higher in the liver fibrosis group, although the differences were not statistically significant. We also found that fibrosis was only related to the level of serum albumin and platelet count ($p \leq 0.05$).

Virological Parameters

The average viral load was higher in patients without liver fibrosis (mean 46.12×10^5) compared to patients with fibrosis (mean 24.88×10^5), even the differences were not statistically significant ($p = 0.914$). HCV genotype was identified in 8 of 15 patients (4 of genotype 3A, and 4 of genotype 1B). In the remaining cases, 3 of the blood samples couldn't be amplified, while the blood sample of rest was not sent for the genotype test.

Histopathological Features

In 2 of 15 cases. (13%), the liver biopsy was histologically normal. Most patients had mild degrees of necroinflammation or score ≤5 (10/15 patients;66%), 12/15 (80%) with normal to mild periportal ± bridging necrosis, 13/15 (87%) with normal to mild intralobular degeneration with focal necrosis and 9/15 (60%) with normal to mild portal inflammation. Summing up the inflammatory components, the mean necroinflammation score in patients with liver fibrosis (mean 5.8) was found to be higher than in patients without fibrosis (mean 2.2), ($p = 0.031$) .

DISCUSSION

It was apparent from this study that out of the clinical, biological, virological and histological parameters in CHC patients with CRF, only the serum albumin and the platelets level were related to the occurrence of liver fibrosis.

Serum aminotransferase levels were generally normal or minimally elevated in CRF patients, compared with non-uremic patients. The low serum aminotransferase in these patients has been attributed to pyridoxal-5'-phosphate (an active form of vitamin B6) deficiency that results in decreased synthesis and release of transminase. Thus, it was suggested that in some studies the upper limits of AST and ALT in patients on HD should be taken at below 20 U/L.[14] The values of aminotransferase levels seen in this study supported previous data, with the mean serum levels of 36 ± 26 and 48 ± 29 and normal serum AST and ALT in 8 of 12 cases (66,6%) and 4 of 12 (33.3%) cases respectively.

Regarding the histological data, it appeared that the liver histology in CHC with CRF patients exhibited a less severe degree of liver injury. Some report found that all liver biopsy specimens showed varying degrees of portal and lobular inflammatory activity[12], with most patients having a minimal or a mild necroinflammatory activity, such as; 76% showing minimal to mild interface inflammatory activity, 81% showing minimal to mild lobular inflammatory. Another study by Cotler SJ et al. confirmed these results with only 4% (2 of 26) of ESRD patients having grade-3 inflammation and 9% (4 of 46) having cirrhosis[10]. The result of a comparison with non-uremic subjects suggested that the grade of inflammation and the prevalence of bridging fibrosis and cirrhosis were significantly lower in ESRD patients. We also found from our study that the mean HAI score was 3.87 ± 3.66, with most cases having normal to mild necroinflammation score, and none having cirrhosis. Such finding

have led some authority to hypothesis that increased hepatocyte growth factor was one explanation for the mild HCV related changes in the liver histology of dialysis patients[15-19].

Regarding any correlation between the clinical, biological, virological to histological features, most studies found no significant relationship between fibrosis in the liver biopsy specimens and other parameters[8,10,12,20,21]. A study in 37 ESRD patients by Martin P et al. showed no significant relationship between disease severity and age, sex, race, alcohol abuse, etiology of renal failure, HCV genotype, HCV RNA, AST, ALT level and duration of HCV infection[12]. Another study in 50 ESRD patients by Sterling RK *et al*. had also found no differences in the mean age, sex, race, or time from the first possible exposure to HCV between patients with bridging fibrosis or cirrhosis compared to those with less advanced histological stages of disease and also confirmed by the study of Cotler SJ *et al*.[8,10] There was also no relationship between HCV-RNA titer and either ALT or Knodell's score in patients with ESRD. But patients with advanced fibrosis were more likely to have had prior RT (54%) compared to those with minimal or no fibrosis (38%).

In our study, we also found there was no significant relationship between fibrosis in the liver biopsy specimens and other parameters, except for the serum albumin and the platelet levels. To the best of our knowledge, there are no publish data that indicate such these results. This may be caused by the small sample sizes, the lack of serial laboratory parameters and the wide normal range of these laboratory levels. There were several important limitations, in our study including the small sample sizes, the lack of serial laboratory parameters and liver biopsy specimens and the estimated duration of CHC infection. An extended study with more collected data would be needed to further clarify the picture.

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