Pathologically Different Features and Fibrosis Scores in Chronic Hepatitis C Genotypes 3 and 1

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Background: *Chronic hepatitis C genotypes 3 and 1 are the two most common genotypes in Thailand.*
Objective: *Identify the pathologically different features between genotypes 3 and 1and to compare the fibrosis score of Knodell HAI and Ishak modified HAI.*
Material and method: *The pathological features of 114 liver biopsies were evaluated.*
Results: *Steatosis was more commonly found in genotype 3 than in genotype 1 (97.1% vs. 77.8%, p = 0.001). Portal lymphoid follicles were commonly found, but bile duct damage was uncommon. The majority of portal tracts showed partial involvement. The majority of patients had Knodell fibrosis 1 and Ishak fibrosis 3.*
Conclusion: *Steatosis is significantly more common in genotype 3, while other features do not show any differences. The portal tracts show partial involvement because inflammatory cells tend to aggregate and form lymphoid follicles. The most comparable fibrosis scores are Knodell fibrosis 1 and Ishak fibrosis 3.*

Keywords: *Steatosis, Pathology, HCV*

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Hepatitis C virus (HCV) has 6 genotypes and more than 90 subtypes with varying geographic distribution. Characteristic features of HCV infection include bile duct damage, intraportal lymphoid follicles, and steatosis[1-16]. However, particular manifestations of each genotype were hypothesized. Recently, comparative studies among genotypes have been reported. One study failed to demonstrate the correlation between HCV genotypes and Knodell histological activity index (HAI), RNA titers or serum alanine aminotransferase (ALT) levels[17], while other studies revealed some differences among genotypes. Steatosis is significantly more common in genotype 3[1,3]. Bile duct injury is common in genotype 1b[18]. Genotype 1b was frequently found in advanced disease[19-20] and seemed to be associated with hepatocellular carcinoma[21-27]. These partially proved the hypothesis about the specific manifestation of each genotype, but until now, no pathognomonic histological features in distinguishing each genotype have been documented. The present study aimed to identify specific histopathological features of HCV genotype 3 and 1, two common genotypes in Thailand[28] that have different treatment responsiveness[29].

Nowadays, there are several histological scoring systems in evaluating chronic hepatitis C with different preferences among clinicians and pathologists. Pathologists in endemic areas of hepatitis B virus who are familiar with Knodell HAI, would also prefer using it in HCV hepatitis. This might cause some difficulty in considering the treatment regimen based on other scoring systems, because the scoring number is different among the systems. Another purpose of the present study was to compare the fibrosis score of two scoring systems, Knodell HAI and Ishak modified HAI.

Material and Method

Patients

One hundred and fourteen patients with chronic hepatitis C genotype 3 or 1 who underwent liver biopsy at the Hepatitis Clinic, Siriraj Hospital from Jan 1997 to Dec 2002 entered the present study. Patients with co-infection of other types of viruses, such as HBV, hepatitis D virus (HDV), HIV infection,

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alcoholic patients (regular drinking of more than 30 gm of alcohol/day), patients using hepatotoxic drugs or herbal medication within 6 months prior to liver biopsy, and patients having DM and hyperlipidemia were excluded.

Anti HCV were determined by microparticle enzyme immunoassay (MEIA; Abbot Axsym system, Wiesbaden, Germany). Genotypes were determined by the VERSANT HCV genotype amplification kit (Bayer Health Care). HCV viral load was quantified by COBAS amplicor HCV monitor test, version 2.0 (Roche diagnostic).

Data collection

Demographic data (age, gender, and clinical symptoms), biochemical data (aspartate aminotransferase (AST), ALT), and serological results (viral load, and viral genotypes) were recorded. Two pathologists reviewed liver biopsies together without any laboratory data. Several histological features were evaluated as follows; degree of steatosis (0: absent, 1: < 33%, 2: 33-66%, 3: > 66%), distribution of steatosis and intralobular degeneration (localized: involved only one zone, diffuse: involved two or three zones), presence of portal lymphoid follicles**,** presence of bile duct damage (lymphocytic intraepithelial or periductular infiltration), the involvement pattern in each portal tracts (total involvement (> 80%), partial involvement (< 80%), no involvement), the Knodell histology activity index and the fibrosis score of the Ishak modified HAI.

Statistical analysis

Results are expressed as mean and standard deviation (SD). The proportions of each factor were compared between the groups by Chi-square's tests and Fisher exact 2-tail tests. The group means were compared by Student's t tests and Mann-Whitney U tests. Differences were considered significant for a p value less than 0.05.

Results

The mean age of the 114 patients was 44.8 years. Males were more common than females. Biochemical and serological results revealed no statistical difference between genotype 3 and 1 (Table1).

Steatosis was significantly more common in genotype 3 than in genotype 1 (97.1% vs. 77.8%, p = 0.001) and distributed diffusely in both genotypes (85.1% in genotype 3, 68.6% in genotype 1). Lymphoid follicles were found in the majority of cases (62.3% in genotype 3, 60% in genotype 1), but bile duct damage was found in a minority of cases (11.6% in genotype 3, 20% in genotype 1) (Table 2).

Lymphoid follicles were found in the majority of cases, however, only some portal tracts were involved in each biopsy (18.5% in genotype 3, 20% in genotype 1). Similarly, bile duct damage was also found only in some portal tracts (12% in genotype 3, 17% in genotype 1) (Table 3).

Most portal tracts in each biopsy were partially infiltrated by inflammatory cells (63.8% in genotype 3, 58.7% in genotype 1), while some portal tracts showed total involvement (28% in genotype 3, 33.9% in genotype 1) and a few portal tracts in the same biopsy showed no inflammation (8.2% in genotype 3, 7.5% in genotype 1). However, the pattern of portal inflammation between the two genotypes was not different (Table 4).

Neither Knodell HAI, grading, staging nor Ishak fibrosis scores revealed any statistical difference between genotype 3 and 1. Most patients had fibrosis in the early stage. The Knodell HAI fibrosis score was 1 and the Ishak fibrosis score was 3 for the majority of both genotypes (Table 5).

Table 1. Demographic data, biochemical and serological results

	genotype 3 (n = 69)	genotype 1 (n = 45)	p-value	Total
Mean age	43.9 ± 10.7	46.2 ± 9.8	0.25	44.8 ± 10.4
Gender (M:F)	37:32	31:14		68:46
AST	103.75 ± 64	85.20 ± 55	0.12	96.43 ± 61
ALT	154.61 ± 94	145.98 ± 87	0.62	151.20 ± 91
Viral load ($x10^6$) Mean ± SD Median [Min-Max]	1.19 [0.011-104.7]	2.74 [0.025-60.85]	0.46	

Table 2. Specific characteristics: steatosis, lymphoid follicles, bile duct damage and distribution of intralobular degeneration

	genotype 3 (n = 69)	genotype 1 (n = 45)	p-value
Steatosis	67 (97.1%)	35 (77.8%)	0.001
Degree of steatosis	2:49:18	10:27:8	0.011
absent:mild:mod/severe	(2.9:71:26.1%)	(22.2:60:17.8%)	
Distribution of steatosis: Diffuse	57 (85.1%)	24 (68.6%)	0.089
Lymphoid follicles	43 (62.3%)	27 (60%)	0.96
Bile duct damage	8 (11.6%)	9 (20%)	0.34
Distribution of intralobular degeneration:	[n = 63]	[n = 43]	
Diffuse	51 (81%)	42 (97.7%)	0.023

Table 3. Percent of portal tracts with lymphoid follicles and bile duct damage

		genotype 3 (n = 43)	genotype 1 (n = 27)	Total (n = 70)
Percent of portal tracts	mean	18.5%	20%	19%
with lymphoid follicles	Range (50% of case)	9-29%	12-27%	10-28%
		genotype 3 (n = 8)	genotype 1 (n = 9)	Total (n = 17)
Percent of portal tracts	mean	12%	17%	15%
with bile duct damage	Range (50% of case)	9-27%	9-25%	9-18%

Table 4. Involvement pattern of portal inflammation

	genotype 3 (n = 69)	genotype 1 (n = 45)	p-value	Total (n = 114)
Percent of portal tracts with partial involvement	63.80 $\pm$ 22.16	58.67 $\pm$ 24.55	0.25	61.77 $\pm$ 23.18
Percent of portal tracts with total involvement	27.97 $\pm$ 20.49	33.85 $\pm$ 25.19	0.18	30.29 $\pm$ 22.54
Percent of portal tracts without inflammation	8.23 $\pm$ 11.10	7.49 $\pm$ 9.65	0.71	7.94 $\pm$ 10.52

Table 5. The Knodell histology activity index and Ishak fibrosis score

	genotype 3 (n = 69)	genotype 1 (n = 45)	p-value
HAI score	6 (1,16)	6 (2,16)	0.3
Periportal inflammation	1 (0,6)	1 (0,6)	0.43
Lobular inflammation	1 (0,4)	1 (0,3)	0.43
Portal inflammation	3 (0,4)	3 (0,4)	0.13
Fibrosis (staging)	1 (0,4)	1 (0,4)	0.41
Activity (grading)	5 (1,12)	5 (1,12)	0.26
Ishak fibrosis score	3 (1,6)	3 (0,6)	0.14

Table 6. Number of patients at treatment cut point (Knodell HAI and Ishak fibrosis score)

	Ishak fibrosis < 3	Ishak fibrosis ≥ 3	Total
HAI fibrosis < 1	13	1	14 (12.28%)
HAI fibrosis ≥ 1	25	75	100 (87.72%)
Total	38 (33.33%)	76 (66.67%)	114

One hundred patients (87.7%) had Knodell HAI fibrosis score 1 or more, compared with seventy-six (66.7%) who had Ishak fibrosis score 3 or more (Table 6).

Discussion

The present study reveals that only steatosis is specific to HCV genotype 3, similar to other previous studies [1-3]. However, other characteristics do not show any statistical difference. In addition, a new interesting feature found in the present study is the involvement pattern of portal inflammation in chronic viral hepatitis C. The majority of HCV patients have partial involvement of portal inflammation. This finding can be explained by the presence of lymphoid follicles or aggregation in chronic viral hepatitis C. However, the involvement pattern could not distinguish between HCV genotype 3 and 1. Further study of its significance will be useful in comparison with chronic viral hepatitis B whose portal tracts tend to be infiltrated diffusely without lymphoid follicles.

A comparison of fibrosis score between the two systems, Knodell HAI and Ishak modified HAI, reveals that there is good correlation between Knodell HAI fibrosis score 1 and Ishak fibrosis score 3. According to the recommended treatment cut point at Ishak fibrosis score 3[30], 76 patients will receive treatment. Compared with 100 patients, if Knodell HAI fibrosis score 1 is accepted as a treatment cut point. This group of patients covers almost all patients who should receive treatment by Ishak criteria. However, a number of patients are over treated if this application is accepted. Nevertheless, it is acceptable by some experts to treat all genotype 3 patients regardless of their fibrosis score because it is the most favorable genotype. In conclusion, HAI fibrosis score 1 could be adopted as a treatment criterion in the areas where the hepatitis C genotype 3 is commonly found.

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ลักษณะทางพยาธิวิทยาและการเกิดพังผืด ในการติดเชื้อไวรัสตับอักเสบ ซี สายพันธุ์ 3 และ 1

อนัญญา มนุญากร, ทวีศักดิ์ แทนวันดี, คณิต อธิสุข

การติดเชื้อไวรัสตับอักเสบ ซี เรื้อรัง สายพันธุ์ 3 และ 1 เป็นสายพันธุ์ที่พบบ่อยที่สุดในประเทศไทย การศึกษานี้เป็นการศึกษาย้อนหลังทำการตรวจลักษณะพยาธิวิทยาของชิ้นเนื้อตับ จากผู้ป่วยทั้งสิ้น 114 ราย พบว่า การพบไขมันในตับ (steatosis) ในผู้ป่วยไวรัสตับอักเสบ ซี สายพันธุ์ 3 พบได้บ่อยกว่า สายพันธุ์ 1 อย่างมีนัยสำคัญทางสถิติ นอกจากนี้ยังพบการกระจายเป็นหย่อมของ lymphocyte ใน portal tracts และมีการรวมตัวเป็นกลุ่มของ lymphoid follicles ได้บ่อยในทั้งสองสายพันธุ์ แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญ ผู้ป่วยส่วนมากทั้งสองสายพันธุ์พบมีพังผืดในระยะเริ่มต้น