Tissue Expression of the Hepatitis C Virus NS3 Protein Does Not Correlate with Histological or Clinical Features in Patients with Chronic Hepatitis C

Wei-Hsuan Liao, MD; Shui-Yi Tung, MD; Cheng-Han Shen, MD; Kam-Fai Lee[1], MD; Cheng-Shyong Wu, MD

Background: In chronic hepatitis B, the HBcAg viral protein in liver tissue demonstrates a positive correlation with serum aminotransferase levels, serum hepatitis B viral DNA, and histological activities. Little is known if similar relationships exist for chronic hepatitis C. This study attempted to determine if expression of the hepatocyte NS3 protein of the hepatitis C virus (HCV-NS3) was correlated with the serum HCV-RNA load, hepatitis activity, or other clinical parameters.

Methods: Clinical and histological data of 214 patients with chronic hepatitis C were retrospectively reviewed. A mouse monoclonal antibody was used to detect HCV-NS3 in hepatocytes. The staining intensity was scored semiquantitatively as 0~3+, and its correlations with the serum HCV-RNA load, hepatitis activity, and other clinical parameters were analyzed.

Results: In total, 202 (94%) of the 214 liver biopsies were positive for HCV-NS3, and the intensity of HCV-NS3 staining was 0 in 12 (6%), 1+ in 181 (84%), and 2+ in 21 patients (10%). The intensity of HCV-NS3 expression in the samples did not correlate with patient age (p = 0.302, ANOVA), patient gender (p = 0.130, Fisher's exact test), the alanine transaminase level (p = 0.177, ANOVA), serum HCV-RNA level (p = 0.305, ANOVA), HCV antibody titer (p = 0.139, Chi-squared test), hepatitis activity index score (p = 0.861, Chi-squared test), or sustained viral response rate (p = 0.861, Chi-squared test).

Conclusions: This HCV-NS3 immunohistochemical staining method was reliable for detecting HCV in liver specimens. Hepatocyte expression of HCV-NS3 was not correlated with the serum viral load, severity of hepatic injury, or treatment response.

(Chang Gung Med J 2011;34:260-7)

Key words: HCV-NS3 antigen, immunohistochemistry, HAI score

Hepatitis C virus (HCV), which infects 170 million people worldwide, leads to chronic hepatitis in 60%~80% of infected patients.[1] HCV is also one of the major risk factors for the development of liver cirrhosis and hepatocellular carcinoma. In Taiwan, the prevalence of HCV was determined to

From the Division of Gastroenterology, Department of Internal Medicine; [1]Department of Pathology, Chang Gung Memorial Hospital at Chiayi, Chang Gung University College of Medicine, Taoyuan, Taiwan.
Received: May 5, 2010; Accepted: Sep. 15, 2010
Correspondence to: Dr. Shui-Yi Tung, Division of Gastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital at Chiayi. 6, W. Sec., Jiapu Rd., Puzih City, Chiayi County 613, Taiwan (R.O.C.) Tel.: 886-5-3821000 ext. 2005; Fax: 886-5-3623005; E-mail: ma1898@cgmh.org.tw

be 4.4% among the general population.[2] Although serological and molecular biological tests are commercially available, a simple and reproducible immunohistochemical (IHC) method that identifies and localizes HCV in normal and pathological liver tissues from humans is still lacking. Previous studies published IHC protocols for HCV detection in liver tissues with good concordance with reverse-transcription polymerase chain reaction (RT-PCR)-based methods, despite the high variability of IHC sensitivity compared to the RT-PCR.[3,4] The development of mouse monoclonal antibodies to the recombinant NS3 protein of HCV make it possible to observe virus-specific staining in the cytoplasm of hepatocytes with acute HCV infections and in immunosuppressed patients with chronic HCV infection.[5,6] The biological role of the nonstructural NS3 protein remains unknown, although some data indicated that the core, NS3, and NS5A proteins promote cell growth via modulation of cell-cycle regulator genes.[3,4]

An IHC analysis of the HBcAg viral protein in the liver during chronic hepatitis B virus (HBV) infection revealed a positive correlation among serum aminotransferase levels, serum HBV DNA loads, and histological activities.[3,4] Hence, detection of this HBV epitope can serve as a marker of HBV replication. Similar observations for HCV were discussed in a number of studies; however, the conclusions are controversial.[6-9] Kasprak et al. showed that the tissue expression of HCV-NS3 did not correlate with the histologic grade or stage in patients with chronic hepatitis C.[6] However, the case number in that previous study was small, and the sensitivity of the IHC method used was limited. As such, the strength of their conclusions might have been limited by these biases. The present study attempted to determine if there were correlations among hepatocyte HCV-NS3 expression, the serum HCV-RNA load, hepatitis activity, and other clinical parameters by employing a large case study and a sensitive IHC method.

METHODS

In total, 513 consecutive patients with chronic hepatitis C were followed at Chang Gung Memorial Hospital, Chiayi, Taiwan, between January 2003 and December 2008. Chronic hepatitis C was defined as being seropositive for antibodies to HCV for more than 6 months based on an enzyme-linked immunosorbent assay (ELISA) (AxSYM HCV vers. 3.0; Abbott, Ludwigshafen, Germany). Medical records of these patients were reviewed, and information on demographic data, hematology, biochemistry, serology, hepatitis markers, HCV genotypes (INNO LiPa HCV II assay; Innogenetics, Zwijnaarde, Belgium), HCV-RNA levels (Amplicor HCV test vers. 2.0 with a sensitivity of 600 IU/mL; Roche, Mannheim, Germany), and liver biopsy histological examinations (hepatitis activity index (HAI) scores) was retrospectively reviewed. Patients with the following conditions were excluded: (1) positive for the hepatitis B surface antigen (HBsAg) or HIV antibodies; (2) evidence of decompensated liver cirrhosis or hepatocellular carcinoma; (3) past antiviral treatment; (4) a known history or serological evidence of autoimmune liver disease, inheritable disorders such as hemochromatosis, or Wilson's disease; (5) excessive alcohol intake (daily alcohol consumption exceeding 30 g) or drug abuse, or (6) no liver biopsy specimen. Six patients with chronic hepatitis B who did not have chronic hepatitis C were enrolled as a control group (HBsAg [+], HCV [-]). Among these 6 patients, 2 had serum alanine transaminase (ALT) levels < 2-fold that of the baseline, 2 had ALT levels of 2~5-fold that of the baseline, and 2 had ALT levels > 5-fold that of the baseline.

Liver biopsy specimens

Transcutaneous needle liver biopsy specimens were collected from treatment-naïve patients with chronic hepatitis C after informed consent was obtained. They were fully informed of the nature of the disease and the diagnostic procedures involved. The length and diameter of the puncture needles were 1.0~3.5 cm and 2~3 mm, respectively. Specimens were then fixed in 10% formaldehyde and embedded in paraffin. After routine tissue processing, a histological diagnosis was made on hematoxylin and eosin-stained sections. The severity of hepatitis and liver fibrosis were evaluated using an HAI system proposed by Knodell et al.[10]

Immunohistochemical staining and semiquantification of the HCV-NS3 protein

To detect the HCV-NS3 antigen, tissue speci-

mens were cut and mounted on slides coated with 3-aminopropyltriethoxysilane (APES). Air-dried frozen sections were placed in 1.5% hydrogen peroxide/methanol for 10 min. After washing in running tap water for 5 min, 1600 mL of 0.01 M sodium citrate buffer (pH 6.0) was brought to a boil in a Prestige stainless steel pressure cooker using a hotplate. When the maximum temperature was reached, sections were incubated in this solution for 1 min and then washed in Tris-buffered saline (TBS) for 5 min. Sections were then placed in diluted normal serum for 20 min and covered with a primary Novocastra mouse monoclonal antibody against HCV-NS3 (Leica Microsystems, Wetzlar, Germany). After 5 min of washing in TBS, sections were incubated in a diluted anti-mouse peroxidase-conjugated antibody for 30 min. After washing in TBS for an additional 5 min, sections were incubated in the appropriate dilution of mouse peroxidase-antiperoxidase (PAP) for 30 min. Sections were then washed in TBS and incubated in diluted diaminobenzidine tetrahydrochloride (DAB). Finally, specimens were counterstained with hematoxylin, dehydrated, covered with a coverslip, and mounted. Specimens were then ready for observation by a pathologist (KF Lee) using a light microscope. The specimen processing steps were performed according to the manufacturer's instructions (Leica Microsystems). The intensity of HCV-NS3 staining present in hepatocytes was semiquantitatively scored as 0~3+: 0, no positively stained cells; 1+, fewer than 33% positive cells; 2+, 34%~66% positive cells; 3+, 67%~100% positive cells/per high-power field (Fig. 1A-C). A tissue sample that was HCV-Ab negative but HBsAg positive was stained as a control (Fig. 1D).

Statistical methods

Analysis of variance (ANOVA), Chi-squared

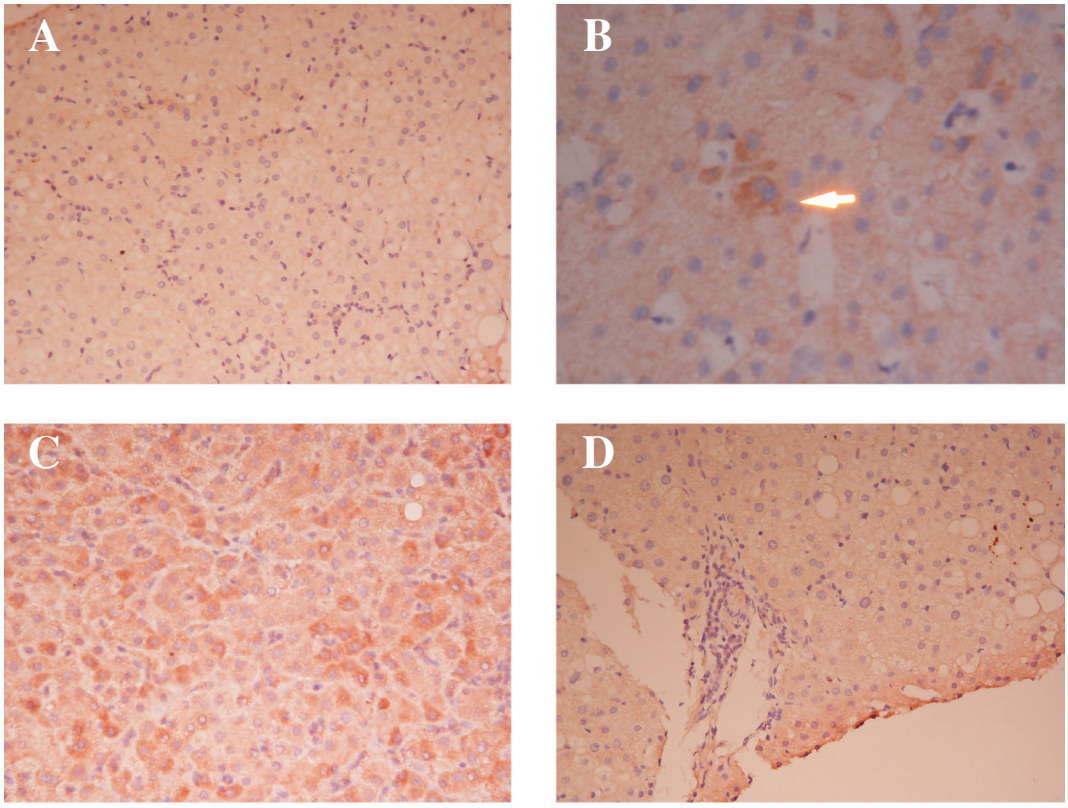

Fig. 1 Representative microscopic images of immunohistochemical staining for the hepatitis C virus (HCV)-NS3 protein in liver biopsy specimens. (A) Score 0, no positively stained cells. (B) Score 1+, < 33% positive cells (arrowhead). (C) Score 2+, 34%~66% positive cells. (D) Negative control. 400 x magnification.

tests, and Kruskal-Wallis tests were used where appropriate. Data analysis was conducted using SPSS version 17 (SPSS, Chicago, IL, U.S.A.). ANOVA was used for continuous data analysis, and the Chi-squired test was used for ordinal data.

RESULTS

Hepatocyte HCV-NS3 expression in patients with chronic hepatitis C

After excluding certain patients based on the conditions described above, 214 patients (114 males and 100 females) with complete data were enrolled in this study. Patient ages ranged 21~79 (57.65 ± 11.1) years at the time of the biopsy. In total, 113 patients were HCV genotype 1, and 97 patients were genotype 2. The clinical characteristics of all patients are summarized in Table 1.

Among the 214 liver specimens from patients positive for HCV-Ab, 202 (94%) stained positive for the HCV-NS3 protein. The intensity of HCV-NS3 staining was 0 in 13 (6%), 1+ in 181 (84%), and 2+ in 21 (10%) patients.

Hepatocyte HCV-NS3 expression in patients with chronic hepatitis B

Six patients with chronic hepatitis B who did not have chronic hepatitis C were enrolled as a control group (HBsAg [+], HCV [-]). Among these 6 patients, 2 had serum ALT levels of < 2-fold the upper limit of ALT, 2 had ALT levels of 2~5-fold the upper limit of ALT, and 2 had ALT levels > 5-fold the upper limit of ALT. Liver tissue samples from these 6 control patients were all negative for HCV-NS3 protein expression. The specificity of the IHC staining method used in this study was 100%.

Hepatocyte HCV-NS3 expression and liver histology

To determine the correlation between the HCV-NS3 staining intensity and other clinicopathological parameters, we further analyzed those parameters relative to the staining scores (Table 2).

In total, 141 (65.6%) had HAI scores of < 11, and 74 (34.4%) patients had scores of > 11. The HAI scores did not increase relative to the hepatocyte HCV-NS3 staining intensity (p = 0.861). We further evaluated the odds ratio (OR) of the degree of the HAI score based on the HCV-NS3 staining intensity.

Table 1. Clinical Characteristics of the 214 Patients in This Study

Age (years)	57.65 ± 11.11
Male: female (no.)	114: 100
AST (U/L)	108.28 ± 62.62
ALT (U/L)	166.74 ± 126.53
HCV-RNA (106 IU/mL)	1.21 ± 2.48
HAI score (10~22)	9.65 ± 2.63
Inflammation score (0~18)	7.07 ± 2.34
Fibrosis score (number, %)	
0	0 (0%)
1	2 (0.93%)
2	100 (46.73%)
3	98 (45.79%)
4	14 (6.54%)
Genotype (1: 2) (no.)	113: 97
Anti-HCV (S/CO) (mean ± S.D.)	36.16 ± 46.82
Non-SVR: SVR (no.)	25: 86*
HCV-NS3 (0+: 1+: 2+) (no.)	12: 181: 21

Abbreviations: AST: aspartate aminotransferase; ALT: alanine transaminase; HCV: hepatitis C virus; HAI: hepatitis activity index; S/CO: sample/cut-off ratio; SVR: sustained viral response; *: Only 111 patients had data for post-treatment HCV-RNA levels.
Data are presented as the number value or mean ± standard deviation (S.D.).

The HAI OR was 0.72 (95% confidence interval (CI): 0.221~2.373, p = 0.592) in the HCV-NS3 staining intensity 0/1 group and 0.968 (95% CI: 0.371~2.520, p = 0.946) in the HCV-NS3 staining intensity 1/2 group. After subdividing the HAI scores into inflammation and fibrosis scores, we still observed no correlation of the staining intensity of the HCV-NS3 protein with liver inflammation or fibrosis (p = 0.700 and 0.959, respectively).

HCV-NS3 expression and serum ALT levels

Serum ALT levels in patients with 0, 1+, and 2+ HCV-NS3 staining were 134.8 ± 76.6, 163.7 ± 119.5, and 211.2 ± 190.1 IU/L, respectively. Serum ALT levels tended to increase as HCV-NS3 staining intensity increased, but this was not statistically significant (p = 0.177, ANOVA).

Table 2. Baseline Characteristics among the Three Groups with Different Staining Intensities

	NS3 protein intensity in liver tissues			
	0 (n = 12)	1 (n = 181)	2 (n = 21)	*p* value
Age (year), mean ± S.D.	60 ± 9.2	57 ± 11.4	60 ± 9.0	0.293*
Gender (male)	4 (33.3%)	102 (56.4%)	8 (38.11%)	0.103†
HCV-RNA (106 IU/mL), median (IQR)	0.47 (0.10~1.62)	0.58 (0.14~1.22)	0.36 (0.07~2.09)	0.854‡
HAI score (≧ 11), *n*	5 (41.7%)	62 (34.3%)	7 (33.3%)	0.861†
Inflammation score, mean ± S.D.	7 ± 2.37	7.02 ± 2.31	7.48 ± 2.64	0.700*
Fibrosis score, mean ± S.D.	2.58 ± 0.67	2.58 ± 0.62	2.62 ± 0.67	0.959*
Genotype n, (%)				
1	7 (58.3%)	98 (54.1%)	7 (33.3%)	0.421†
2	5 (41.7%)	79 (43.6%)	13 (61.9%)	
Others§	0	4 (2.2%)	1 (0.8%)	
ALT (U/L), mean ± S.D.	134.75 ± 76.55	163.72 ± 119.46	211.19 ± 190.13	0.177*
Anti-HCV, *n* = 204, median (IQR)	60.29 (10.26~142.02)	36.69 (1.44~180.68)	18.23 (6.29~77.41)	0.139‡
SVR				
No *n* = 25	1 (0.9%)	23 (20.7%)	1 (0.9%)	0.861†
Yes *n* = 86	3 (2.7%)	77 (69.4%)	6 (5.4%)	

Abbreviations: IQR: interquartile range; *: ANOVA; †: Chi-squared test; ‡: Kruskal-Wallis test; §: Genotype others: 1 case with mixed 1b and 6a; 2 cases with mixed G1 and G2; 1 case with 6a; and 1 case with G2 and G5.

Hepatocyte HCV-NS3 expression and the serum anti-HCV titer

The mean serum anti-HCV titers (sample/cutoff (S/CO) ratios) in patients with 0, 1+, and 2+ NS3 staining were 60.29, 36.69, and 18.23, respectively. Serum S/CO ratios tended to increase as the HCV-NS3 staining intensity increased, but this was not statistically significant ($p = 0.139$).

Hepatocyte NS3 expression and the serum HCV RNA load

Mean serum HCV RNA levels of patients with 0, 1+, and 2+ HCV-NS3 staining were 0.47×10^6, 0.58×10^6, and 0.36×10^6 IU/mL, respectively. Serum HCV RNA levels did not increase as the HCV-NS3 staining intensity increased ($p = 0.854$, ANOVA).

Hepatocyte HCV-NS3 expression and the treatment response

Among the participants in this study, 111 patients received standard treatment of pegylated interferon plus ribavirin for chronic hepatitis C and had complete virology data, and 86 (77.48%) of these patients achieved a sustained viral response. The staining intensity of the HCV-NS3 protein in liver tissues did not significantly differ between patients with a successful or failed response ($p = 0.861$, Chi-squared test).

DISCUSSION

Detection and localization of HCV in liver tissues are vital for diagnostic purposes and clinical management of patients infected with HCV, and to elucidate viropathological mechanisms. The fragility of HCV-RNA and the low levels of viral expression in infected tissues are substantial limitations to molecular assays for HCV characterization. HCV antigen detection in liver biopsies by IHC is an attractive option for the precise localization and quantification of viral proteins and allows direct access to histological patterns. Currently, there are few IHC methods targeting specific HCV proteins, such as NS3, NS4a,

NS5a, and NS5b.[5-9] Among these proteins, HCV-NS3 expression in hepatocytes is known to correlate well with the presence of HCV RNA in liver tissue.[11] Therefore, the HCV-NS3 protein should be a good indicator of the viral load in the liver. In this study, HCV-NS3 staining demonstrated a high sensitivity (94%) for detecting hepatocyte HCV.

Several studies investigated the association between the severity of liver disease and HCV proteins in liver tissues, and their conclusions were controversial. Attallah et al. found that the NS4 detection rate increased with the progression of liver disease.[12] Galy et al. also showed that stronger E2 glycoprotein staining was related to more-advanced liver fibrosis.[13] On the other hand, other studies did not demonstrate similar findings. Kasprak et al. found that tissue expressions of HCV-NS3 and core proteins did not correlate with the histologic grade or stage of liver tissues in patients with chronic hepatitis C.[6] As the case number in that previous study was not large and the sensitivity of the IHC staining method was low, the role of IHC staining in HCV proteins probably could not be fully exhibited. In the present study, we used a more-sensitive method and enrolled a larger number of patients; however, our results still showed that hepatocyte HCV-NS3 expression did not correlate with the severity of liver disease. We also found that the intensity of hepatocyte HCV-NS3 expression did not correlate with serum ALT levels, anti-HCV S/CO ratios, or HCV RNA levels. These findings imply that liver damage caused by HCV might not be directly cytopathic or dose-dependent. To validate the use of hepatocyte HCV protein expression as a marker of disease severity, a further understanding of the pathogenesis of HCV-related liver injury is needed.

Recent publications showed that an IHC assessment of HCV antigens is a good tool for differentiating and managing acute liver injury after liver transplantation.[14] However, no previous study investigated the correlation between hepatocyte HCV antigen expression and treatment outcomes. We attempted to determine if the intensity of hepatocyte HCV-NS3 expression was an outcome predictor for HCV treatment in this study, but we did not observe a positive correlation.

In summary, IHC staining of hepatocyte HCV proteins is a sensitive tool for identifying the presence of HCV in patients with chronic hepatitis. The intensity of HCV protein staining, however, did not correlate with the histological severity, serum HCV RNA load, ALT level, anti-HCV S/CO ratio, or treatment outcome. Further investigations into the pathogenesis of HCV-related liver injury are warranted.

Acknowledgements

This study was supported by Chang Gung Memorial Hospital, Chiayi, Taiwan.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
2. Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B Virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J Formos Med Assoc 2007;106:148-55.
3. Pal S SM, Thomassen L, Emerson SS, Su T, Feuerborn N, Kae J, Gretch DR. Intrahepatic hepatitis C virus replication correlates with chronic hepatitis C disease severity in vivo. J Virol 2006;80:2280-90.
4. Siavoshian S, Abraham JD, Kieny MP, Schuster C. HCV core, NS3, NS5A and NS5B proteins modulate cell proliferation independently from p53 expression in hepatocarcinoma cell lines. Arch Virol 2004;149:323-6.
5. Kyono K, Miyashiro M, Taguchi I. Expression and purification of a hepatitis C virus NS3/4A complex, and characterization of its helicase activity with the scintillation proximity assay system. J Biochem 2004;135:245-52.
6. Kasprzak A, Biczysko W, Adamek A, Wysocki J, Zabel M, Jurczyszyn D, Chmielewski M, Surdyk-Zasada J. Studies on tissue expression of HCV proteins (NS3 and C) in chronic hepatitis C using the ImmunoMax technique. Scan J Gastroenterol 2004;39:387-8.
7. Ghosh AK, Steele R, Meyer K, Ray R, Ray RB. Hepatitis C virus NS5A protein modulates cell cycle regulatory genes and promotes cell growth. J Gen Virol 1999;80:1179-83.
8. Chu CM, Shyu WC, Liaw YF. Immunopathology on hepatocyte expression of HBV surface, core, and x antigens in chronic hepatitis B: clinical and virological correlation. Dig Dis Sci 2010;55:446-51.
9. Ramakrishna B, Mukhopadhya A, Kurian G. Correlation of hepatocyte expression of hepatitis B viral antigens with histological activity and viral titer in chronic hepatitis B virus infection: an immunohistochemical study. J Gastroenterol Hepatol 2008;23:1734-8.
10. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active

hepatitis. Hepatology 1981;1:431-5.
11. Nepomnyashchikh GI, Aidagulova SV, Nepomnyashchikh DL, Tolokonskaya NP, Karavaeva YY, Sakharova EG, Mezentseva GA, Batemirova EV. Immunohistochemical, molecular, and pathomorphological study of liver biopsy specimens during chronic hepatitis C. Bull Exp Biol Med 2002;134:307-11.
12. Attallah AM, Ismail H, Shiha GE, Abou-Dobara MI, El-Sherbiny RE, El-Dosoky I. Immunochemical identification and partial characterization of a native hepatitis C viral non-structural 4 antigen in sera of HCV infected patients. Clin Chim Acta 2008;388:115-22.
13. Galy O, Petit MA, Benjelloun S, Chevallier P, Chevallier M, Srivatanakul P, Karalak A, Carreira C, Lyandrat N, Essaid A, Trepo C, Hainaut P, Chemin I. Efficient hepatitis C antigen immunohistological staining in sections of normal, cirrhotic and tumoral liver using a new monoclonal antibody directed against serum-derived HCV E2 glycoproteins. Cancer Lett 2007;248:81-8.
14. Asanza CG, García-Monzón C, Clemente G, Salcedo M, García-Buey L, García-Iglesias C, Bañares R, Alvarez E, Moreno-Otero R. Immunohistochemical evidence of immunopathogenetic mechanisms in chronic hepatitis C recurrence after liver transplantation. Hepatology 1997;26:755-63.

肝組織上 C 型肝病毒 NS3 蛋白質表現與肝切片病理分級或臨床肝炎活性不相關

廖威宣 董水義 沈建亨 李錦輝[1] 吳正雄

背 景： 慢性 B 型肝炎的患者，其肝組織上的 HBcAg 已被證實與血清中的 ALT 高低、DNA 高低及肝組織病理上受損程度有正相關。然而在慢性 C 型肝炎患者，少有人探討有無類似的關係。本項研究目的在於探討，C 肝病毒的 NS3 蛋白質在肝組織上的染色強度是否和臨床上一些常用的 C 型肝炎檢測有相關。

方 法： 本研究共收集了 214 位慢性 C 型肝炎病人的臨床資料、血清學資料和肝切片。利用針對 NS3 蛋白質的單株抗體來做肝組織上的 NS3 免疫組織化學染色，將染色強度由 0至 3+ 半定量化後，分析染色強度是否和血清中的 HCV-RNA，AST，ALT 高低以及肝切片的 HAI score 有正相關。

結 果： 在 214 位病人中，共有 204 位可染出，敏感度達 94%。半定量的染色強度在 2+ 的有 21 位 (10%)，在 1+ 的 181 位 (84%)，有 12 位未能染出 (6%)，沒有病人的切片可達強度 3+ 者。經分析，染色強度和病人的年紀 (p = 0.302, ANOVA test)，性別 (p = 0.130, Fisher's exact test)，ALT 高低 (p = 0.177, ANOVA test)，血清 RNA 量 (p = 0.305, ANOVA test)，血清 HCV 抗體高低 (p = 0.139, Chi-square test)，肝切片 HAI score (p = 0.861, Chi-square test)，或是治療反應 (sustained viral response) (p = 0.861, Chi-square test) 皆無相關。

結 論： 因爲高敏感度，肝切片上的 NS3 蛋白質免疫組織化學染色法提供我們一項 C 型肝病毒的檢測法。然而，其染色強度和血清中的病毒量，肝炎活性，肝組織受損程度均無正相關，在對於慢性 C 型肝炎治療的反應預測方面也沒有幫助。慢性 C 型肝炎的致病機轉需要更多的研究，本染色法或許可以是一項不錯的工具。

(長庚醫誌 2011;34:260-7)

關鍵詞： C 型肝炎病毒 NS3 蛋白質，免疫組織化學染色法，HAI 分數

長庚醫療財團法人嘉義長庚紀念醫院 內科部 肝膽胃腸科，[1]病理科；長庚大學 醫學院
受文日期：民國99年5月5日；接受刊載：民國99年9月15日
通訊作者：董水義醫師，長庚醫療財團法人嘉義長庚紀念醫院 內科部 肝膽胃腸科。嘉義縣613朴子市嘉朴路西段6號。
Tel.: (05)3821000轉2005; Fax: (05)3623005; Email: ma1898@cgmh.org.tw