World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i29.3704

World J Gastroenterol 2010 August 7; 16(29): 3704-3708
ISSN 1007-9327 (print)
© 2010 Baishideng. All rights reserved.

BRIEF ARTICLE

Is autoimmune hepatitis a frequent finding among HCV patients with intense interface hepatitis?

Rosilene G Badiani, Vitória Becker, Renata M Perez, Carla AL Matos, Lara B Lemos, Valéria P Lanzoni, Luis Eduardo C Andrade, Alessandra Dellavance, Antonio Eduardo B Silva, Maria Lucia G Ferraz

Rosilene G Badiani, Vitória Becker, Carla AL Matos, Lara B Lemos, Antonio Eduardo B Silva, Maria Lucia G Ferraz, Division of Gastroenterology, Federal University of Sao Paulo, 04023-900, Sao Paulo, Brazil
Renata M Perez, Department of Internal Medicine, Federal University of Rio de Janeiro, 21941-913, Rio de Janeiro, Brazil
Valéria P Lanzoni, Department of Pathology, Federal University of Sao Paulo, 04023-900, Sao Paulo, Brazil
Luis Eduardo C Andrade, Alessandra Dellavance, Immunology Group, Fleury Medicine and Health, 04344-903, Sao Paulo, Brazil
Author contributions: Badiani RG, Becker V, Lemos LB and Matos CAL collected all the human material and performed the research; Andrade LEC, Dellavance A and Lanzoni VP provided reagents and analytical tools and were also involved in editing the manuscript; Badiani RG, Perez RM, Silva AEB and Ferraz MLG designed the study, analyzed the data and wrote the manuscript.
Supported by CAPES research support agency, Brazil
Correspondence to: Maria Lucia G Ferraz, Professor, Division of Gastroenterology, Federal University of Sao Paulo, 04023-900, Sao Paulo, Brazil. marialucia.ferraz@fleury.com.br
Telephone: +55-11-50147426 Fax: +55-11-50147425
Received: February 1, 2010 Revised: March 20, 2010
Accepted: March 27, 2010
Published online: August 7, 2010

Abstract

AIM: To evaluate the overlap of autoimmune hepatitis in hepatitis C virus (HCV)-infected patients with intense interface hepatitis.

METHODS: Among 1759 patients with hepatitis C submitted to liver biopsy, 92 (5.2%) presented intense interface hepatitis. These patients were evaluated regarding the presence of antinuclear antibody (ANA), anti-smooth muscle antibody (SMA) and anti-liver/kidney microsomal antibody (LKM-1), levels of γ-globulin and histological findings related to autoimmune hepatitis (plasma cell infiltrate and presence of rosettes).

RESULTS: Among patients with hepatitis C and intense interface hepatitis there was a low prevalence of autoantibodies (ANA = 12%, SMA = 5%, LKM-1 = 0%) and the median γ-globulin level was within the normal range. Typical histological findings of autoimmune disease were observed in only two cases (2%). After applying the score for diagnosis of autoimmune hepatitis, only one patient was classified with a definitive diagnosis of autoimmune hepatitis. Since overlap with autoimmune hepatitis was not the explanation for the intense necroinflammatory activity in patients with chronic hepatitis C we sought to identify the variables associated with this finding. The presence of intense interface hepatitis was associated with more advanced age, both at the time of infection and at the time of the biopsy, and higher prevalence of blood transfusion and alcohol abuse.

CONCLUSION: Although possible, overlap with autoimmune hepatitis is a very rare association in HCV-infected patients with intense interface hepatitis, an unusual presentation which seems to be related to other host variables.

© 2010 Baishideng. All rights reserved.

Key words: Hepatitis C; Liver biopsy; Antinuclear antibody; Autoimmune hepatitis; Interface hepatitis

Peer reviewer: Dr. Eli Magen, Allergy and Clinical Immunology, Medicine B, Barzilai Medical Center, Ashdod 77456, Israel

Badiani RG, Becker V, Perez RM, Matos CAL, Lemos LB, Lanzoni VP, Andrade LEC, Dellavance A, Silva AEB, Ferraz MLG. Is autoimmune hepatitis a frequent finding among HCV patients with intense interface hepatitis? *World J Gastroenterol* 2010; 16(29): 3704-3708 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i29/3704.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i29.3704

INTRODUCTION

Hepatitis C is the main cause of liver-related morbidity and mortality and represents a worldwide public health problem[1]. An estimated 170 million individuals are infected with hepatitis C virus (HCV), corresponding to 3% of the world population[2].

Infection with HCV is characterized by a high chronicity rate (70% to 85%)[3-6], progression to cirrhosis in 20% to 30% of cases[1,6-8] and the development of hepatocarcinoma in 5% of patients[9]. In addition, this infection represents the most common indication for liver transplantation worldwide[10].

Histological analysis of patients chronically infected with HCV usually reveals some degree of fibrosis, generally associated with the presence of mild or moderate necroinflammatory activity[11]. However, a histological pattern demonstrating intense interface hepatitis has been reported[12,13]. In these cases a possible association with autoimmune hepatitis has been suggested, raising doubts regarding the correct diagnosis and the establishment of adequate treatment[14-16]. The objective of the present study was to evaluate the overlap with autoimmune hepatitis in HCV-infected patients with intense interface hepatitis.

MATERIALS AND METHODS

Patients

Patients chronically infected with HCV followed up at the Federal University of Sao Paulo between 1993 and 2006, who were submitted to a liver biopsy, were studied. The inclusion criteria were chronic infection with HCV (characterized by HCV-RNA positivity) and the presence of intense interface hepatitis upon histological analysis. Patients previously treated or who were HBsAg-positive were excluded.

A control group consisting of patients chronically infected with HCV, who presented absent, mild or moderate interface hepatitis, was included in order to evaluate if an eventual association of autoimmune hepatitis with hepatitis C was restricted to patients with intense necroinflammatory activity. In the absence of such association, a comparison with the control group was performed to evaluate other factors possibly related to intense interface hepatitis. This control group was randomly selected from the database of the Hepatitis Outpatient Clinic of the Federal University of Sao Paulo (1:1 ratio). The same exclusion criteria were adopted for the control group. For the comparative analysis, patients with associated diseases [human immunodeficiency virus (HIV), end-stage renal disease and kidney transplant] were excluded from both groups.

The study was approved by the local Ethical Committee.

Epidemiological characteristics

The patients were evaluated regarding gender, age, estimated duration of infection, age at the time of infection, abusive alcohol consumption (men > 40 g/d and women > 20 g/d), the presence of parenteral risk factors (intravenous drug use, hemodialysis or blood transfusion before 1992) and associated diseases (HIV, end-stage renal disease and kidney transplant). This information was recovered from charts where the data were systematically evaluated with a standardized questionnaire. The duration of infection was evaluated in patients with parenteral risk factors and was estimated from the first year of intravenous drug use or hemodialysis or from the year of first transfusion in patients who had received blood transfusions before 1992.

Laboratory tests

The liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT) and alkaline phosphatase were assayed by an automated kinetic method and were expressed as the following index: value obtained/upper limit of normal. γ-globulins were assayed by electrophoretic fractionation on agarose gel and densitometry. All biochemical tests were performed within a period of 3 mo from the date of the liver biopsy.

Antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-liver/kidney microsomal antibody (anti-LKM) and anti-mitochondrial antibody were determined by indirect immunofluorescence and the titer was considered significant when higher than 1/40.

The patients were tested for the presence of HBsAg and anti-HIV-1/2 using commercial kits (Abbott Laboratories, Chicago, IL, USA). Anti-HCV was determined with a third-generation enzyme immunoassay (Abbott Laboratories, Chicago, IL, USA). Qualitative HCV-RNA was detected by PCR using the Amplicor® Hepatitis C Virus Test, version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA), with a detection limit of 50 IU/mL. HCV genotyping was performed by VERSANT HCV Genotype Assay - LiPA (Innogenetics N.V., Belgium).

Histological analysis

A liver biopsy was indicated in all patients, irrespective of ALT levels. Liver tissue fragments were obtained by percutaneous biopsy with a Tru-cut® needle. The liver biopsy slides were stained with hematoxylin-eosin, Masson's trichrome, Prussian blue (Perls' stain), and silver for reticular fibers (Gomori's stain), and were reviewed by a single pathologist who was unaware of the clinical data. Histological analysis included the determination of the grade of interface hepatitis and of the stage of fibrosis, which were assessed using a semiquantitative scoring system according to Ludwig[17]. Patients were classified as having intense interface hepatitis if they presented a score of periportal activity = 4, in a scale varying from 0 (no inflammation) to 4 (intense necroinflammatory activity).

In order to better characterize the presence of eventual histological components suggestive of autoimmune injury, the presence of plasma cell infiltrate and rosettes was also analyzed.

Scoring system for diagnosis of autoimmune hepatitis

All patients were evaluated regarding the reviewed interna-

Table 1 General characteristics of patients with intense interface hepatitis *n* (%)

	Intense interface hepatitis (*n* = 92)
Male gender	52 (57)
Age (mean ± SD, yr)	49.8 ± 10.5
Age at the time of infection (mean ± SD, yr)	29.5 ± 9.8
Parenteral risk factor	59 (64)
Duration of infection (mean ± SD, yr)	20.1 ± 8.7
History of blood transfusion	44 (48)
Intravenous drug use	13 (14)
Hemodialysis	2 (2)
Alcoholism	25 (27)
Human immunodeficiency virus-positive	5 (5)
Renal transplant	6 (7)
End-stage renal disease	2 (2)
Alanine aminotransferase (xULN)	4.1 (0.3-18.2)
Aspartate aminotransferase (xULN)	3.0 (0.9-10.4)
γ-glutamyltransferase (xULN)	4.1 (0.1-16.4)
Alkaline phosphatase (xULN)	0.9 (0.3-3.8)
γ-globulin (g/dL)	1.9 (0.73-5.74)
Antinuclear antibody	11 (12)[1]
Anti-smooth muscle antibody	5 (5)
Anti-liver/kidney microsomal antibody	0 (0)
Antimitochondrial antibody	1 (1)
Hepatitis C virus genotype	
Genotype 1	53/77 (69)
Genotype non-1	24/77 (31)
Cirrhosis	53 (58)
Parenchymatous activity ⩾ 3	50 (54)
Intense plasma cell infiltrate	2 (2)
Rosettes	26 (28)

[1]All antinuclear antibody positive patients presented the speckled pattern; titers varied from 1/80 to 1/640. xULN: Times the upper limit of normal.

tional diagnostic criteria for autoimmune hepatitis according to the International Autoimmune Hepatitis Group[18].

Statistical analysis

The χ^2 test and Fisher's exact test were used for statistical analysis of categorical variables. Numerical variables were compared between the two groups using the Student *t*-test and Mann-Whitney test. A level of significance of 0.05 (α = 5%) was adopted.

RESULTS

Among the 1759 patients chronically infected with HCV submitted to a liver biopsy during the study period, 92 presented intense interface hepatitis, corresponding to 5.2% of the initial sample. The characteristics of these patients are shown in Table 1.

Among patients presenting intense interface hepatitis, there was a low prevalence of autoantibodies and the median γ-globulin level was within the normal range. Typical histological findings of autoimmune disease were observed in only two cases (2%). After applying the scoring system for diagnosis of autoimmune hepatitis only one patient was classified as having a definitive diagnosis.

Since overlap with autoimmune hepatitis was not the explanation for the intense necroinflammatory activity in patients with chronic hepatitis C, we sought to identify the variables associated with this finding. Therefore, we compared epidemiological, laboratory and histological characteristics between patients with intense interface hepatitis and a randomly selected control group consisting of chronic HCV-infected patients with absent, mild or moderate interface hepatitis. For comparison between groups, 13 patients with associated disease were excluded from the group with intense interface hepatitis: 6 patients with kidney transplant, 5 with HIV co-infection and 2 with end-stage renal disease.

Table 2 Comparative analysis of general characteristics between groups *n* (%)

	Group 1 (*n* = 79)	Group 2 (*n* = 79)	*P*
Male gender	44 (56)	49 (62)	0.42
Mean age (mean ± SD, yr)	50.8 ± 10.6	43.9 ± 11.5	< 0.001
Alcoholism	22 (28)	10 (13)	0.02
Blood transfusion	37 (47)	23 (29)	0.02
Intravenous drug use	10 (13)	9 (11)	0.81
Duration of infection (mean ± SD, yr)	22.2 ± 7.9	20.9 ± 7.5	0.49
Age at the time of infection (mean ± SD, yr)	28.6 ± 9.6	23.0 ± 11.2	0.02
ALT (xULN)	4.2 (0.3-18.2)	1.8 (0.9-11.3)	< 0.001
AST (xULN)	3.1 (0.9-10.4)	1.4 (0.8-5.8)	< 0.001
GGT (xULN)	3.8 (0.1-16.4)	1.1 (0.1-10.6)	< 0.001
Alkaline phosphatase (xULN)	0.8 (0.3-2.1)	1.0 (0.1-3.0)	0.32
γ-globulin (g/dL)	1.9 (0.7-4.0)	1.7 (0.9-3.7)	0.19
ANA positive	9 (11)	7 (9)	0.59
Genotype 1	43/65 (66)	54/79 (68)	0.78
Cirrhosis	50 (63)	20 (25)	< 0.001
Parenchymatous activity ⩾ 3	43 (55)	3 (4)	< 0.001

Group 1: Patients with intense interface hepatitis; Group 2: Patients with absent, mild or moderate interface hepatitis. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyltransferase; xULN: Times the upper limit of normal; ANA: Antinuclear antibody.

In the group of patients with intense interface hepatitis, the subjects were older and the proportions of blood transfusion and abusive alcohol consumption were higher. In addition, these patients presented higher levels of ALT (4.2 *vs* 1.8, $P < 0.001$), AST (3.1 *vs* 1.4, $P < 0.001$) and GGT (3.8 *vs* 1.1, $P < 0.001$). No difference in the proportion of patients with reactive ANA or serum γ-globulin levels was observed between groups (Table 2).

Regarding liver biopsy, the mean number of portal tracts observed was 11. Histological aspects are presented in Table 2. The proportion of patients with moderate to intense lobular necroinflammatory activity and cirrhosis was higher in the group with intense interface hepatitis ($P < 0.001$).

DISCUSSION

Previous studies have demonstrated that the presence of intense interface hepatitis in patients chronically infected with HCV is rare[19,20]. When this finding is present, other liver diseases, especially autoimmune hepatitis, should be carefully ruled out. In the present study, 1759 patients

chronically infected with HCV were initially evaluated and in 92 of them (5.2%) a liver biopsy revealed intense interface hepatitis, indicating that, although uncommon, this finding might be a histological pattern of hepatitis C.

The main objective of the present study was to evaluate the overlap with autoimmune hepatitis in HCV-infected patients with intense interface hepatitis. In this sample only two patients (2%) had serological and histological evidence of autoimmunity in the group with intense interface hepatitis and only one patient had a definitive diagnosis of autoimmune hepatitis based on the International Autoimmune Hepatitis Group scoring system[18]. Although a 12% prevalence of ANA was found among the intense interface hepatitis patients, there was no difference in the proportion of patients with positive ANA when they were compared to patients with less intense necroinflammatory activity. In addition, the prevalence of SMA and anti-LKM was very low in the group with intense interface hepatitis.

No histological lesions typical of autoimmune hepatitis were identified in all except two patients and the proportion of cases presenting a significant plasma cell infiltrate was very low in patients with intense interface hepatitis. The high proportion of patients with rosettes observed in the group with intense interface hepatitis was not considered as suggestive of autoimmune injury, since it reflects hepatic regeneration activity as a consequence of greater necroinflammatory activity and can be observed in other etiologies of liver disease[21,22]. These findings support the suggestion that overlap with autoimmune hepatitis is a very rare association in HCV-infected patients with intense interface hepatitis and raises the possibility that some mechanism related to the host-virus interaction might be responsible for the intense interface hepatitis observed.

Since overlap with autoimmune hepatitis was not found in association with intense necroinflammatory activity in patients with chronic hepatitis C we sought to identify other variables associated with this finding.

In comparison to the control group, the presence of intense interface hepatitis was associated with the following epidemiological characteristics: more advanced age both at the time of infection and at the time of the biopsy, and a higher prevalence of blood transfusion and alcohol abuse. With respect to age at the time of infection, a higher necroinflammatory hepatic activity was observed in patients with more advanced age at HCV infection[19,23]. However, the mechanisms related to this phenomenon are still unknown. One hypothesis is that the ability of the immune system to contain the pathological process triggered by the HCV infection declines with age. It is possible that the higher proportion of patients with a history of blood transfusion in the group with intense interface hepatitis, another association observed in this study, also reflects the association between more advanced age and intense interface hepatitis, since in this sample patients with a history of transfusion were older ($P = 0.025$).

Excessive alcohol consumption was another variable associated with intense interface hepatitis, suggesting that alcohol may modify the histological injury induced by HCV[23,24], rendering the disease more aggressive even in the absence of lesions characteristic of direct alcoholic hepatic disease. The mechanism whereby alcohol may aggravate the HCV-induced inflammatory process remains obscure.

Analysis of biochemical and histological characteristics demonstrated that patients with intense interface hepatitis present with more severe liver disease, including a high proportion of cirrhosis (63%). With respect to liver enzymes, significantly higher ALT, AST and GGT levels were observed, an expected finding since elevated aminotransferases[25] and GGT[26] levels have been shown to be associated with greater hepatic inflammatory activity.

Although an association between genotype 1 and more intense necroinflammatory activity has been demonstrated[27], no such association between HCV genotype and severity of liver disease was observed in the present study and in most of the studies reported in the literature[28-32].

Regarding histological findings, the histological variables associated with intense interface hepatitis were advanced fibrosis and more intense parenchymatous activity. Although the association between necroinflammatory activity and fibrosis is controversial, this finding supports the hypothesis that necroinflammatory activity influences the progression of hepatic fibrosis as demonstrated in other studies[33-36]. The parenchymatous activity was another variable independently associated with intense interface hepatitis. Although the interface hepatitis is the main histological lesion observed in chronic hepatitis C, whenever the necroinflammatory activity is intense, this process tends to involve all the compartments, and is not restricted to the portal tract.

In conclusion, the absence of elevated γ-globulin levels, the low prevalence of autoantibodies, the occurrence of typical histological findings of autoimmune disease in only two cases (2%), and a definitive diagnosis according to the autoimmune hepatitis score in only one case, suggest that overlap with autoimmune hepatitis is a very rare association in HCV-infected patients with intense interface hepatitis. The uncommon histological presentation of hepatitis C with intense interface hepatitis seems to be related mainly to other host variables.

COMMENTS

Background

Previous studies have demonstrated that intense interface hepatitis is an uncommon finding in chronic hepatitis C. When this finding is present, it raises doubt regarding a possible association with autoimmune hepatitis.

Research frontiers

The main objective of the present study was to evaluate the overlap with autoimmune hepatitis in hepatitis C virus (HCV)-infected patients with intense interface hepatitis.

Innovations and breakthroughs

This study demonstrated that overlap with autoimmune hepatitis is a very rare association in HCV-infected patients with intense interface hepatitis. This finding raises the possibility that some mechanism related to the host-virus interaction might be responsible for this histological pattern.

Applications

Considering that overlap with autoimmune hepatitis in HCV-infected patients with intense interface hepatitis is very uncommon, the best clinical approach for these patients should be antiviral therapy. These results reduce the dilemma of

whether immunosuppressive therapy is indicated for patients presenting with this histological finding.

Terminology

Interface hepatitis is a histological finding in liver biopsies observed in chronic hepatitis. It is also termed necroinflammatory periportal activity and was formerly known as piecemeal necrosis. Interface hepatitis is graded as mild, moderate or intense. In this study the authors aimed to evaluate HCV-infected patients with intense interface hepatitis.

Peer review

The paper is well written and represents timely research aimed at identifying a link between hepatitis C and autoimmune hepatitis.

REFERENCES

1 **Alberti A**, Benvegnù L. Management of hepatitis C. *J Hepatol* 2003; **38** Suppl 1: S104-S118
2 **National Institutes of Health**. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. *Hepatology* 2002; **36**: S3-S20
3 **Hoofnagle JH**. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997; **26**: 15S-20S
4 **Alter MJ**, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999; **341**: 556-562
5 **Villano SA**, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999; **29**: 908-914
6 **Alter HJ**, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000; **20**: 17-35
7 **Lauer GM**, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52
8 **Seeff LB**. Natural history of chronic hepatitis C. *Hepatology* 2002; **36**: S35-S46
9 **Tong MJ**, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995; **332**: 1463-1466
10 **Seaberg EC**, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in the United States from 1987-1998: updated results from the Pitt-UNOS Liver Transplant Registry. *Clin Transpl* 1998; 17-37
11 **Jármay K**, Karácsony G, Ozsvár Z, Nagy I, Lonovics J, Schaff Z. Assessment of histological features in chronic hepatitis C. *Hepatogastroenterology* 2002; **49**: 239-243
12 **Roudot-Thoraval F**, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. *Hepatology* 1997; **26**: 485-490
13 **Pasquale G**, Sagnelli E, Coppola N, Onofrio M, Scarano F, Scolastico C, Bellomo PF, Lettieri A, Mogavero AR, Caprio N, Sagnelli C, Piccinino F. [An attempt to improve classification of HCV-correlated chronic hepatitis] *Infez Med* 2005; **13**: 16-22
14 **Cassani F**, Cataleta M, Valentini P, Muratori P, Giostra F, Francesconi R, Muratori L, Lenzi M, Bianchi G, Zauli D, Bianchi FB. Serum autoantibodies in chronic hepatitis C: comparison with autoimmune hepatitis and impact on the disease profile. *Hepatology* 1997; **26**: 561-566
15 **Czaja AJ**, Carpenter HA. Histological findings in chronic hepatitis C with autoimmune features. *Hepatology* 1997; **26**: 459-466
16 **Antonaci S**, Giannelli G, Simone B, Vella FS. [Syndrome of overlap: Chronic hepatitis C/autoimmune hepatitis: fact or fancy?] *Recenti Prog Med* 2005; **96**: 27-31
17 **Ludwig J**. The nomenclature of chronic active hepatitis: an obituary. *Gastroenterology* 1993; **105**: 274-278
18 **Alvarez F**, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Büschenfelde KH, Zeniya M. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; **31**: 929-938
19 **Delladetsima JK**, Rassidakis G, Tassopoulos NC, Papatheodoridis GV, Smyrnoff T, Vafiadis I. Histopathology of chronic hepatitis C in relation to epidemiological factors. *J Hepatol* 1996; **24**: 27-32
20 **Sood A**, Midha V, Sood N, Kaur H, Malhotra V, Awasthi G. Chronic hepatitis C in northern India--the pathological and clinical spectrum. *J Assoc Physicians India* 2004; **52**: 380-384
21 **Bach N**, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992; **15**: 572-577
22 **Czaja AJ**, Carpenter HA. Sensitivity, specificity, and predictability of biopsy interpretations in chronic hepatitis. *Gastroenterology* 1993; **105**: 1824-1832
23 **Gomes de Sá Ribeiro Mde F**, da Costa Gayotto LC, de Alencar Fischer Chamone D, Strauss E. Alcoholic intake predisposes to more interface hepatitis in chronic hepatitis C. *Ann Hepatol* 2005; **4**: 176-183
24 **Hézode C**, Lonjon I, Roudot-Thoraval F, Pawlotsky JM, Zafrani ES, Dhumeaux D. Impact of moderate alcohol consumption on histological activity and fibrosis in patients with chronic hepatitis C, and specific influence of steatosis: a prospective study. *Aliment Pharmacol Ther* 2003; **17**: 1031-1037
25 **Pradat P**, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, Badalamenti S, Trépo C. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology* 2002; **36**: 973-977
26 **Silva IS**, Ferraz ML, Perez RM, Lanzoni VP, Figueiredo VM, Silva AE. Role of gamma-glutamyl transferase activity in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol* 2004; **19**: 314-318
27 **Svirtlih N**, Delic D, Simonovic J, Jevtovic D, Dokic L, Gvozdenovic E, Boricic I, Terzic D, Pavic S, Neskovic G, Zerjav S, Urban V. Hepatitis C virus genotypes in Serbia and Montenegro: the prevalence and clinical significance. *World J Gastroenterol* 2007; **13**: 355-360
28 **Booth JC**, Foster GR, Levine T, Thomas HC, Goldin RD. The relationship of histology to genotype in chronic HCV infection. *Liver* 1997; **17**: 144-151
29 **Adinolfi LE**, Utili R, Andreana A, Tripodi MF, Rosario P, Mormone G, Ragone E, Pasquale G, Ruggiero G. Relationship between genotypes of hepatitis C virus and histopathological manifestations in chronic hepatitis C patients. *Eur J Gastroenterol Hepatol* 2000; **12**: 299-304
30 **Mohsen AH**. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001; **48**: 707-713
31 **Poynard T**, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. *J Hepatol* 2001; **34**: 730-739
32 **Silva GF**, Nishimura NF, Coelho KI, Soares EC. Grading and staging chronic hepatitis C and its relation to genotypes and epidemiological factors in Brazilian blood donors. *Braz J Infect Dis* 2005; **9**: 142-149
33 **Yano M**, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, Hashimoto E, Lefkowitch JH, Ludwig J, Okuda K. The long-term pathological evolution of chronic hepatitis C. *Hepatology* 1996; **23**: 1334-1340
34 **Fontaine H**, Nalpas B, Poulet B, Carnot F, Zylberberg H, Brechot C, Pol S. Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. *Hum Pathol* 2001; **32**: 904-909
35 **Ghany MG**, Kleiner DE, Alter H, Doo E, Khokar F, Promrat K, Herion D, Park Y, Liang TJ, Hoofnagle JH. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003; **124**: 97-104
36 **Lagging LM**, Westin J, Svensson E, Aires N, Dhillon AP, Lindh M, Wejstål R, Norkrans G. Progression of fibrosis in untreated patients with hepatitis C virus infection. *Liver* 2002; **22**: 136-144

S- Editor Wang YR **L- Editor** Logan S **E- Editor** Zheng XM