OTHER

Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis

Clin Gastroenterol Hepatol 2004 Jul; 2(7):625-31.

Kessler WR, Cummings OW, Eckert G, Chalasani N, Lumeng L, Kwo PY.

BACKGROUND & AIMS: Autoimmune hepatitis is a common cause of chronic hepatitis, and acute presentation is thought to be uncommon. The aim of this study was to compare clinical, biochemical, and histological features in patients with autoimmune hepatitis presenting with either acute or chronic hepatitis.

METHODS: Retrospective review of all patients with autoimmune hepatitis presenting to a University medical center from 1993 to 2002.

RESULTS: One hundred fifteen patients with autoimmune hepatitis were identified. Ten patients with autoimmune hepatitis were identified as having acute presentation (group I), and 20 patients with a classic presentation as chronic hepatitis (group II) served as age- and sex-matched controls. All patients met criteria published by the International Autoimmune Hepatitis Group. Patients with acute presentation differed significantly with regard to encephalopathy, albumin levels, and bilirubin levels. Blinded liver biopsy review demonstrated that those with acute presentation had significantly less fibrosis, and significantly greater interface hepatitis, lobular disarray, lobular hepatitis, hepatocyte necrosis, zone III necrosis, and submassive necrosis.

CONCLUSIONS: In our study, patients with an acute presentation of autoimmune hepatitis differed from patients with a classical presentation clinically, biochemically, and histologically. In our review, a majority of patients with acute autoimmune hepatitis presented with fulminant hepatic failure. The pattern of zone 3 necrosis may be a specific finding in those with acute autoimmune hepatitis.

Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth

Pediatr Infect Dis J 2004 Jul; 23(7):650-5.

Petersen KM, Bulkow LR, McMahon BJ, Zanis C, Getty M, Peters H, Parkinson AJ.

BACKGROUND: The duration of protection after hepatitis B vaccination of infants is unknown.

METHODS: We determined antibody to hepatitis B surface antigen (anti-HBs) at 4-13 years of age in 363 low risk children who had been vaccinated starting at birth with hepatitis B vaccine. Those with nonprotective titers (<10 mIU/mL) received a booster dose. We similarly followed 16 children of hepatitis B surface antigen (HBsAg)-positive mothers.

RESULTS: Of low risk infants receiving a plasma-derived vaccine, 41% (42 of 102) of those whose primary response was unknown and 24% (4 of 17) who had initially responded retained protective titers (> or = 10 mIU/mL) of anti-HBs at 9 and 13 years, respectively. Of those who did not have protective antibody titers, 61% (33 of 54) and 67% (8 of 12), respectively, responded to a booster dose. In children of HBsAg-positive mothers, 31% retained protective anti-HBs

at 12 years, and 90% (9 of 10) with nonprotective titers responded to a booster. In low risk children initially receiving a recombinant vaccine, 12.5% (26 of 208) and none (0 of 36) retained protective anti-HBs titers at 5 and 7 years of age, respectively. Of those who did not have protective titers, 90% (120 of 134) and 91% (32 of 35), respectively, responded to a booster.

CONCLUSIONS: Anti-HBs disappeared by 5 years of age in most children who were vaccinated with hepatitis B vaccine from birth. Although most children showed immunologic memory, one-third failed to demonstrate an anamnestic response to a booster dose. Additional long term studies of low risk infants are needed to determine duration of protection and the necessity for or timing of booster doses.

Analysis of 388 cases of primary sclerosing cholangitis in Japan; Presence of a subgroup without pancreatic involvement in older patients

Hepatol Res 2004 Jul; 29(3):153-159.

Takikawa H, Takamori Y, Tanaka A, Kurihara H, Nakanuma Y.

We analyzed 388 cases of primary sclerosing cholangitis (PSC) in Japan, according to a questionnaire sent to gastroenterologists. There was male predominance (59%), and interestingly there were two peaks in the age distribution as seen in the previous study. Jaundice and itching, major symptoms in PSC patients included in the diagnostic criteria, were observed only 28 and 16%, respectively. Alkaline phosphatase level was less than twofold of the upper limit of the normal range in 35%. In this regard, the diagnostic criteria in 2003 from Mayo Clinic, including cholestatic symptoms and two to three-fold increases in serum alkaline phosphatase, should be modified in Japan. Inflammatory bowel diseases were complicated in 37%, and autoimmune pancreatitis (AIP) in 7.2%. PSC cases with inflammatory bowel diseases were younger than the average, creating the first peak in the age distribution, and have similar characteristics compared to patients with PSC in foreign countries. By contrast, those with AIP, who were more than 50 years old, responded well to corticosteroid therapy. In addition, even after the exclusion of cases of sclerosing cholangitis complicated with AIP, the second peak in the age distribution was clearly evident. Therefore, we conclude that PSC patients without apparent involvement of the pancreas are present in the older patients and seem to be specific in Japan.

Safety and efficacy of hepatitis B surface antigen-pulsed dendritic cells in human volunteers

Hepatol Res 2004 Jul; 29(3):136-141.

Fazle Akbar SM, Furukawa S, Onji M, Murata Y, Niya T, Kanno S, Murakami H, Horiike N.

Hepatitis B surface antigen (HBsAg)-pulsed murine spleen dendritic cells (DCs) have shown tremendous therapeutic potentials in chronic hepatitis B virus (HBV) carriers however, there has been no study regarding the feasibility of using HBsAg-pulsed DCs in human. Five human healthy volunteers with no apparent concomitant diseases were enrolled in this study. DCs were enriched from peripheral blood of each volunteer in endotoxin-free and sterilized conditions. HBsAg-pulsed DCs were prepared by culturing DCs with a commercial-available human grade vaccine containing HBsAg. After assessing the expression of HLA DR and CD86 on HBsAg-pulsed DCs, 5 million HBsAg-pulsed DCs were injected intradermally, once, to each volunteer. The volunteers were serially observed for safety and efficacy of administration of HBsAg-pulsed DCs. No evidence of physical, biochemical, and immunological abnormalities were documented in any volunteer during the next 28 days following administration of HBsAg-pulsed DCs. A single administration of HBsAg-pulsed DCs resulted in upregulation of anti-HBs in two anti-HBs^{+} volunteers. Moreover, anti-HBs were detected in two anti-HBs^{-} volunteer, 2 weeks after administration of HBsAg-pulsed DCs. This study provides the scientific and ethical basis for using HBsAg-pulsed DCs for therapeutic and prophylactic purposes in patients with chronic hepatitis B and non-responders to hepatitis B vaccine, respectively.

Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance

Gut 2004;53:1020–1023

G Donati, B Stagni, F Piscaglia, N Venturoli, A M Morselli-Labate, L Rasciti, L Bolondi

BACKGROUND: The conditions associated with fatty liver disease presenting with normal liver enzymes and the mechanism involved in its development remain to be fully elucidated.

AIMS: The aim of the present study was to test the hypothesis that fatty liver with normal liver enzymes occurs more frequently in arterial hypertensive patients and to establish whether this condition is associated with insulin resistance.

PATIENTS: A total of 55 non-obese, non-diabetic, non-heavy alcohol drinking patients with arterial hypertensive and normal liver enzymes and 55 sex and age matched healthy subjects were enrolled into the study. Methods: Plasma metabolic parameters, body mass index, and the presence of fatty liver were investigated. Insulin resistance was estimated from plasma insulin and glucose as the homeostasis model assessment index. Stepwise logistic regression and multivariate regression analysis were used on the combined sample to identify variables independently associated with fatty liver and insulin resistance.

RESULTS: Hypertensive patients had a significantly higher prevalence of fatty liver (30.9% v 12.7%; p, 0.041), higher insulin resistance (mean 2.27 (SD 1.81) v 1.56 (0.70); p = 0.022), and slightly higher body mass index (24.9 (3.0) v 24.0 (2.2); p = 0.043) than controls. Multivariate logistic regression identified insulin resistance (odds ratio 1.66 (95% confidence interval (CI) 1.03–2.52)) and body mass index (OR 1.22 (95% CI 1.00–1.49)) as factors independently associated with fatty liver. Multivariate regression analysis showed insulin resistance to be predicted by alanine transaminase (p = 0.002), presence of arterial hypertension (p = 0.029), and body mass index (p = 0.048).

CONCLUSion: The higher prevalence of non-alcoholic fatty liver in non-obese hypertensive patients with normal liver enzymes appears to be related to increases in insulin resistance and body weight.

Factors Associated With Receiving Hepatitis B Vaccination Among High-risk Adults in the United States: An Analysis of the National Health Interview Survey, 2000.

Fam Med. 2004 Jul; 36(7):480-6.

BACKGROUND AND OBJECTIVES: Although an effective vaccine against hepatitis B has been licensed in the United States since 1981, and successful childhood vaccination programs have been implemented, hepatitis B virus transmission continues to occur among high-risk adults. In this study, we identified factors associated with receipt of one or more doses of hepatitis B vaccine among adults at high risk for hepatitis B infection.

METHODS: We analyzed data from the 2000 National Health Interview Survey of selected adults ages 18-49 years who were at high risk for hepatitis B infection (n=1,036). Multivariable regression analysis was conducted to determine factors independently associated with vaccination.

RESULTS: Although more than 80% (n=841) of high-risk adults reported previous visits to a clinician during the past year, only 30% (n=498) of men and 31% (n=538) of women reported having received a single dose of hepatitis B vaccine. Young age (18-29 years), never being married, past blood donation, and past human immunodeficiency virus (HIV) testing were independently associated with receiving vaccination for men. For women, young age (18-29 years) and previous vaccinations were significant factors associated with vaccination receipt. Additionally, having a primary care source (men) and seeing an obstetrician-gynecologist provider in the past year (women) were significantly associated with vaccination.

CONCLUSIONS: Hepatitis B vaccination rates for high-risk adults are low, and missed opportunities are frequent. Additional strategies are needed to increase immunization rates of adults at high risk for hepatitis B.

Clinical Outcomes and Disease Progression among Patients Coinfected with HIV and Human T Lymphotropic Virus Types 1 and 2

Clin Infect Dis 2004 Jul 15; 39(2):256-63.

Beilke MA, Theall KP, O'Brien M, Clayton JL, Benjamin SM, Winsor EL, Kissinger PJ.

The goal of this study was to investigate clinical outcomes and survival probabilities among persons coinfected with human immunodeficiency virus (HIV) and human T lymphotropic viruses types 1 and 2 (HTLV-I/II). A nonconcurrent cohort study of 1033 HIV-infected individuals was also conducted. Sixty-two patients were coinfected with HTLV-I, and 141 patients were coinfected with HTLV-II. HTLV-I/II coinfection was highly associated with African-American race/ethnicity, age of >36 years, higher CD4(+) T cell count at baseline and over time, and history of injection drug use. Coinfected patients were more likely to have neurologic complications, thrombocytopenia, respiratory and urinary tract infections, and hepatitis C. Despite having higher CD4(+) T cell counts over time, there was no difference in the incidence of opportunistic infections. Progression to both acquired immunodeficiency syndrome (AIDS; adjusted hazard ratio [aHR], 0.50; 95% confidence interval [CI], 0.25-0.98) and death (aHR, 0.57, 95% CI, 0.37-0.89) were slower among HTLV-II-coinfected patients, compared with time-entry- and CD4(+) T cell count-matched control subjects. In conclusion, HIV-HTLV-I/II coinfection may result in improved survival and delayed progression to AIDS, but this happens at the expense of an increased frequency of other of clinical complications.

Hepatitis C Virus nonstructural protein NS3 interacts with LMP7, a component of immunoproteasome, and affects its proteasome activity

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Khu YL, Tan YJ, Lim SG, Hong W, Goh PY.

NS3, a nonstructural protein of the hepatitis C virus (HCV), contains a protease and a helicase domain and plays essential roles in the processing of the viral polyprotein, viral RNA replication and translation. LMP7, a component of the immunoproteasome was identified as an NS3-binding protein from yeast two-hybrid screens and this interaction was confirmed by in vitro binding and co-immunoprecipitation. The minimal domain of interaction was defined to be between the prosequence region of LMP7 (a.a. 1-40), and the protease domain of NS3. To elucidate the biological importance of this interaction, we studied the effect of this interaction on NS3 protease activity and on LMP7-immunoproteasome activity. Recombinant LMP7 did not have any effect on NS3 protease activity in vitro. The peptidase activities of LMP7-immunoproteasomes, however were markedly reduced when tested in a stable cell line containing a HCV subgenomic replicon (30). The down regulation of proteasome peptidase activities could interfere with the processing of viral antigens for presentation by major histocompatibility complex (MHC) class I molecules and may thus protect HCV from host immune surveillance mechanisms to allow persistent infection by the virus.

Lichen planus induced by hepatitis B vaccination: a new case and review of the literature

Int J Dermatol 2004 Aug; 43(8):562-4.

Calista D, Morri M.

Case Report In May 1996, as part of his routine antihepatitis B (hepB) vaccination plan, a 28-year-old HbsAg-negative man, hospital worker, received his first dose (20 micro g) of a recombinant vaccine (EngerixB-B, Smith Kline and Beecham, Belgium), administered via deltoid injection. The patient was otherwise healthy and taking no medication. Thirty days after the 2nd booster dose, several pruritic, polygonal, purple, papules appeared on the volar aspect of the patient's wrists. New lesions gradually spread to the arms and trunk (Fig. 1). The clinical diagnosis of lichen

planus (LP) was confirmed by histology, which revealed hyperorthokeratosis, hypergranulosis, vacuolar degeneration of the basal layer cells and a dense, band-like lymphocytic infiltrate in the superficial dermis. The disease started to heal after treatment with topical clobetasol propionate 0.05% and sun exposure during the following summer. Five days after the 3rd booster dose, in November 1996, the dermatosis relapsed on the forearms, trunk, and legs. On that occasion, routine laboratory tests, including a complete blood count, blood chemistry and liver function tests, were within normal limits. Screening serologic tests for autoantibodies including antinuclear antibodies, antidouble-stranded DNA, anti-SS-A, anti-SS-B and anti-Sm were all negative. As a result of the inadequate levels of antihepatitis B antibodies, less than 10 IU/l in May 1998, in a high-risk patient who was frequently exposed to blood and its products, an additional booster dose was performed. Three days later a new recurrence of disseminated lichen planus occurred. The patient was successfully treated with prednisone 1 mg/kg/day for 2 weeks. There was no recurrence the following year.

Prevalence and Predictors of Herbal Medication Use in Veterans with Chronic Hepatitis C

Journal of Clinical Gastroenterology Aug, 2004 38(7):605-610.

Siddiqui, Uzma MD; Weinshel, Elizabeth H MD, FACG; Bini, Edmund J MD, MPH

OBJECTIVE: Herbal therapies are used by a substantial proportion of persons in the United States, and use of these supplements may be even higher in those with chronic liver disease. The aims of this study were to prospectively determine the proportion of US veterans with chronic hepatitis C that are currently taking vitamins and herbal medications and to evaluate factors associated with use of herbal preparations.

METHODS: Patients with hepatitis C who were seen in the gastroenterology, infectious disease, and primary care clinics at the VA New York Harbor Healthcare System were invited to participate in this prospective study. For comparison, healthy patients without hepatitis C were enrolled from the primary care clinics at the same medical center. Patients were interviewed by trained research coordinators who obtained detailed demographic and clinical data, as well as information on the use of antioxidants (vitamin C and E), multivitamins, and herbal medications.

RESULTS: Use of vitamin C (34.8% vs. 19.6%, P < 0.001), vitamin E (25.8% vs. 13.2%, P < 0.001), multivitamins (43.6% vs. 28.0%, P < 0.001), and herbal therapies (21.0% vs. 10.4%, P < 0.001) was significantly higher in the 500 patients with hepatitis C compared with the 250 healthy controls. The most common herbal medications taken by hepatitis C patients were milk thistle (12.2%), ginseng (4.6%), and echinacea (3.0%). After adjusting for age and gender, multivariate logistic regression identified 12 or more years of education (OR 2.7; 95% CI 1.6-4.3; P < 0.001) and annual income of at least $20,000 (OR 2.0; 95% CI 1.3-3.2; P = 0.004) as the only significant predictors of herbal medication use in patients with hepatitis C.

CONCLUSIONS: The use of herbal preparations is prevalent among veterans with chronic hepatitis C, especially those with higher levels of education and higher incomes. Obtaining a detailed medical history and documentation of the use of these supplements is critical to determine the potential for herbal-drug interactions and hepatotoxicity.

Viral Gene Sequences Reveal the Variable History of Hepatitis C Virus Infection among Countries.

J Infect Dis 2004 Sep 15; 190(6):1098-108. Epub 2004 Aug 10.

Nakano T, Lu L, Liu P, Pybus OG.

BACKGROUND: The analysis of molecular phylogenies estimated from the gene sequences of sampled viruses can provide important insights into epidemiological processes.

Methods: The demographic and migration histories of the prevalent hepatitis C virus (HCV) subtypes 1a and 1b were inferred from viral gene sequences sampled in 5 countries. Estimated viral phylogenies were analyzed by use of methods based on parsimony and coalescent theory.

ResultsP: The parsimony migration analysis suggested that the global subtype 1a and 1b epidemics are geographically structured, with asymmetrical movement of HCV strains among the sampled countries. The coalescent analysis indicated that subtype 1a infections in the United States, Brazil, and Indonesia began to increase exponentially during the 1940s and 1950s, whereas in Vietnam the increase began after the 1970s. In contrast, subtype 1b infections in these 4 countries and in Japan began to increase exponentially between 1880 and 1920, with a possible recent decrease in infection rates in Indonesia and Japan. In the United States, Brazil, and Vietnam, the epidemic growth rates for subtype 1a strains were higher than those for subtype 1b strains, whereas the growth rates were similar in Indonesia.

CONCLUSIONS: The estimated histories of migration and population growth indicated that patterns of HCV transmission differ among countries and viral subtypes. vitamin E (25.8% vs. 13.2%, P < 0.001), multivitamins (43.6% vs. 28.0%, P < 0.001), and herbal therapies (21.0% vs. 10.4%, P < 0.001) was significantly higher in the 500 patients with hepatitis C compared with the 250 healthy controls. The most common herbal medications taken by hepatitis C patients were milk thistle (12.2%), ginseng (4.6%), and echinacea (3.0%). After adjusting for age and gender, multivariate logistic regression identified 12 or more years of education (OR 2.7; 95% CI 1.6-4.3; P < 0.001) and annual income of at least $20,000 (OR 2.0; 95% CI 1.3-3.2; P = 0.004) as the only significant predictors of herbal medication use in patients with hepatitis C.

CONCLUSIONS: The use of herbal preparations is prevalent among veterans with chronic hepatitis C, especially those with higher levels of education and higher incomes. Obtaining a detailed medical history and documentation of the use of these supplements is critical to determine the potential for herbal-drug interactions and hepatotoxicity.

Liver transplantation for hepatitis B

Hepatology Research 2004 Aug; 29(4): 193-201

Steven-Huy Bui Han , Paul Martin

Recurrent HBV is almost universal post-LT and is accompanied by significant graft and patient loss in the absence of effective immunoprophylaxis. Hepatitis B immunoglobulin (HBIG) monotherapy and lamivudine monotherapy significantly reduce the rate of recurrent hepatitis B, but recurrent hepatitis B still occurs in up to 25% due to the emergence of resistant mutants. Combination administration of HBIG and lamivudine is more efficacious in preventing recurrent hepatitis B, decreasing recurrence rates of hepatitis B to 0–18% in studies. Future studies to determine the optimal dosing regimen and duration of HBIG and lamivudine and to evaluate the efficacy of newer antivirals such as adefovir dipivoxil in preventing recurrent HBV are needed. Treatment of established recurrent hepatitis B remains problematic. Lamivudine has shown promise during the initial treatment period, but is plagued by rapid development of viral resistance with longer treatment duration. Adefovir dipivoxil appears very promising, and further studies are needed to evaluate its efficacy in the post-liver transplant patient. Interferon-alfa's use in the post-liver transplant patient is limited given the availability of the newer antiviral drugs. Famciclovir and ganciclovir have shown some promise in treating recurrent HBV, but have been replaced by newer agents such as lamivudine and adefovir.

The fluctuations of viral load and serum alanine aminotransferase levels in chronic hepatitis

Hepatology Research 2004 Sep; 30(1): 11-17

Hiroshi Ito, Kentaro Yoshioka, Koji Ukai, Kazumasa Watanabe, Motoyoshi Yano, Masatoshi Ishigami, Tetsuya Mizutani, Yumihiko Sasaki, Yoshiaki Katano and Hidemi Goto

Although viral load of hepatitis C virus (HCV) is a predictor of response to interferon therapy, little is known about its fluctuations. We assessed its fluctuations and their correlation with serum alanine aminotransferase (ALT) levels. Viral load was prospectively measured bimonthly for 22 months in 109 patients. In 40 patients, viral load changed more than five fold. Changes were transient and always returned to the baseline levels. ALT levels changed more than three fold in 30 patients. Changes of viral load accompanied simultaneous changes of ALT levels in only 7 of 40 patients with changes of viral load. Mean viral load in 22 months was significantly correlated with mean ALT levels inversely (r = 0.278, P = 0.0036). Mean viral load was significantly higher in 27 patients with persistently normal ALT levels (452.0 ± 342.5 pg/ml) than in 30 patients with changes of ALT levels (202.4 ± 215.0 pg/ml) (P = 0.0016) and than in 52 patients without changes of ALT levels (301.1 ± 295.4 pg/ml) (P = 0.0458). Inverse correlation of viral load with ALT levels suggests that viral load is in suppression by inflammatory activity. However, changes of ALT levels infrequently accompanied simultaneous changes of viral load and vice versa, as often seen in chronic hepatitis B virus infection.

Rebound hepatitis following withdrawal of immunosuppressive therapy in patients with chronic Hepatitis B viral infections

Hepatology Research 2004 Sep; 30(1): 4-10

G. Y. Minuk, J. Rempel, P. Wong, M. Zhang, S. Wong, W. W. S. Wong, A. Meyers and J. Uhanova

Background: Rebound hepatitis is a potentially life-threatening complication of withdrawal from immunosuppressive therapy in patients with chronic Hepatitis B viral (HBV) infections.

Objectives: To document the incidence of rebound hepatitis and determine whether the hepatitis is associated with serologic evidence of immunological rebound or the appearance of specific mutations in the HBV genome.

Methods: Serum cytokines (IL-6, IL-10, TNF- alfa and INF-gama) were documented by enzyme linked immunoassays and previously described HBV mutants (surface, core, pre-core and basal core promoter) by signal probe hybridization analysis in chronic HBV carriers treated with either 6 weeks of prednisone followed by 6 weeks of acyclovir (PR/AC, n = 20) or placebo/placebo (PL/PL, n = 20).

Results: Rebound hepatitis (serum ALT > 2X baseline) occurred in 6/20 (30%) PR/AC patients versus 2/20 (10%) PL/PL recipients (P = 0.24). Serum cytokine levels were similar in those who developed rebound hepatitis compared to those who did not. HBV mutants were absent prior to and during treatment but developed in the follow-up period in three patients. All three patients were PR/AC recipients and in each case, the HBV mutation was in the basal core promoter gene. In two of the three patients, the mutant appeared just prior to the onset of rebound hepatitis while in the third, rebound hepatitis did not occur.

Conclusions: The results of this study indicate an association exists between some cases of rebound hepatitis and the development of HBV mutants.

Detection of serum and intrahepatic KL-6 in anti-HCV positive patients with hepatocellular carcinoma

Hepatology Research 2004 Sep; 30(1): 24-33

Mitsuhiko Moriyama, Hiroshi Matsumura, Azuma Watanabe, Hitomi Nakamura, Yasuo Arakawa, Shuh Oshiro, Hiroshi Aoki, Toshihiro Shimizu, Hiroaki Yamagami, Miki Kaneko, Atsuo Shioda, Naohide Tanaka and Yasuyuki Arakawa

We investigated the clinical significance of serum and intrahepatic KL-6/MUC1 (KL-6) in patients with hepatitis C virus (HCV) antibody-positive hepatocellular carcinoma (HCC). The subjects included 76 patients diagnosed with anti-HCV positive HCC, 69 with, and 51 without, liver cirrhosis (LC). Frozen serum samples were obtained from each subject to determine the serum KL-6 levels using an enzyme-linked immunosorbent assay. Expression of KL-6 antigen in the liver was also investigated using immunoperoxidase staining. The mean serum KL-6 level in patients with HCC was 329.6±213.0ÊU/Êml (319ÊU/Êml for HCC with LC, 342.8ÊU/Êml for HCC without LC). Serum KL-6 levels in patients with HCC with LC and HCC without LC did not differ. Serum KL-6 levels were elevated with increases in the size of spaces occupied by tumors in the liver. Among patients with HCC, there was no correlation between serum KL-6 levels and alpha-fetoprotein (AFP) levels and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels. However, some patients with low levels of AFP and PIVKA-II possessed high levels of KL-6. Furthermore, serum KL-6 levels decreased after therapy for HCC nodules. Immunohistochemical staining showed KL-6 antigen was detected within the cell membrane and in the cytoplasm of cancer cells. KL-6 antigen was localized on the membrane and the endoplasmic reticulum of cancer cells in the cancerous foci by electron microscopy. Our results suggest that serum KL-6 levels represent a serological marker of HCC development, because KL-6 expression was localized to the cancer cells in HCC nodules.