COMPLICATION

Spontaneous regression of hepatocellular two carcinoma: case reports and a literature review

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Kato H, Nakamura M, Muramatsu M, Orito E, Ueda R, Mizokami M.

Spontaneous regression of a malignant tumor is extremely rare. Here we report two cases of spontaneous regression of hepatocellular carcinoma (HCC), and review the associated literature. Case 1 was a 77-year-old male with HCC in the right lobe and multiple lung metastases. -fetoprotein (AFP) and protein induced by vitamin K deficiency or antagonist II (PIVKA-II) were >50,000 ng/ml and 21,500 mAU/ml, respectively. He and his family refused further treatment, and he was discharged. Four months after the diagnosis, dramatic diminution of HCC and lung metastases was noted, and the HCC had disappeared completely 12 months later. Case 2 was a 72-year-old male with multiple nodular regions with enhanced circumference in the right lobe, the largest of which was 8 cm in diameter, referred to the gastroenterology unit of our hospital. Laboratory analyses showed positive for hepatitis C virus antibody, and AFP and PIVKA-II were 936.3 ng/ ml and 2,380 mAU/ ml, respectively. However, he and his family refused further treatment, and he was followed-up as an outpatient by a local clinic. Two years later, radiological investigations revealed remarkable regression of HCC. Laboratory analyses showed that PIVKA-II had decreased to the normal range, while AFP had increased to double the original value.

Activation of fibronectin gene expression by hepatitis B virus x antigen

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Norton PA, Reis HM, Prince S, Larkin J, Pan J, Liu J, Gong Q, Zhu M, Feitelson MA.

The development of fibrosis and cirrhosis during chronic hepatitis B virus (HBV) infection correlates with the persistent expression of HBV x antigen (HBxAg), which acts in part, by stimulating selected signal transduction pathways, including nuclear factor B (NF-B). To identify NF-B responsive genes that are differentially expressed in HBxAg-positive cells, HepG2 cells were stably transfected with HBxAg, and then with pZeoSV2 or pZeoSV2-IB. When RNAs from each culture were compared by PCR-select cDNA subtraction, fibronectin (FN) mRNA was shown to be strongly down-regulated by IB. Up-regulated expression of FN and co-expression between FN and HBxAg were observed in liver sections from HBV carriers that were stained for HBxAg and analysed for FN mRNA by inÊsitu hybridization (ISH). In liver cell cultures, HBxAg increased the levels of FN mRNA and protein. This was because of the HBxAg-mediated trans-activation of the FN promoter, which was NF-B-dependent. HBxAg also antagonized the repression of the FN promoter by the tumour suppressor, p53. Hence, the FN gene may be a natural target for HBxAg trans-activation, perhaps through activation of NF-B and inactivation of p53, thereby contributing to the accumulation of FN in the liver over the course of chronic HBV infection.

Lymphoproliferative disorders in chronic hepatitis C

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R. Idilman A. Colantoni, N. De Maria, S. Alkan, S. Nand and D. H. Van Thiel

Chronic hepatitis C virus (HCV) infection is associated with the development of lymphoproliferative disorders (LPDs). The aim of this investigation was to determine the prevalence and characterization of monoclonal gammopathy and benign and malignant LPDs in individuals with chronic hepatitis C. A total of 233 subjects diagnosed with chronic hepatitis C (male/female ratio: 131/102, median age; 49 years) were studied. Serum and urine were examined for the presence

of a monoclonal gammopathy. A bone marrow aspirate and biopsy was obtained in individuals with a monoclonal gammopathy. Thirty-two patients (13.7%, 32 of 233) had a monoclonal gammopathy; 75% of them were benign and were not associated with malignant disorders (24 of 32) while 25% were associated with malignant LPDs or a plasma cell disorder (eight of 32). Two additional subjects without monoclonal gammopathy were diagnosed as having a malignant LPDs. The prevalence of malignant LPDs/plasma cell disorder in individuals with HCV-induced chronic liver disease was 4.3%. No difference was found in terms of disease duration, HCV genotype, viral load, alanine aminotransferase level or histopathologic score between the subjects with or without a monoclonal gammopathy. The presence of mixed cryoglobulinaemia was strongly associated with the presence of an underlying malignant disorder. Hence a monoclonal gammopathy is found in 14% of patients with chronic hepatitis C and is associated with malignant B-cell LPD in more than a quarter of such patients. The prevalence of LPDs in individuals with HCV-induced chronic liver disease is greater than that of the normal healthy population.

Preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma

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Omagari K, Honda S, Kadokawa Y, Isomoto H, Takeshima F, Hayashida K, Mizuta Y, Murata I, Kohno S.

BACKGROUND: The long-term prognosis of hepatocellular carcinoma (HCC) remains poor and the prediction of survival is often difficult because of the limited liver function and frequent recurrence of HCC in most patients. Therefore, a prognostic classification of HCC should account for both tumor-related variables and liver function.

METHODS: The value of reported prognostic factors for HCC was assessed and a new prognostic classification was established called the 'SLiDe' scoring system (S, stage; Li, liver damage; De, des-gamma-carboxy prothrombin) using 'stage' and 'liver damage' of the recently revised 4th edition of the Japanese staging system edited by the Liver Cancer Study Group of Japan, and the serum level of des-gamma-carboxy prothrombin (DCP) in 177 patients with HCC.

RESULTS: Univariate analysis identified Child-Pugh stage, liver damage, tumor morphology, portal vein thrombosis, stage, serum level of alpha-fetoprotein (AFP), serum level of DCP, and initial treatment as significant prognostic factors. Of these, liver damage, stage, and serum level of DCP remained independent predictive factors of survival after multivariate prognostic analysis using the proportional hazards regression model. Therefore, a new prognostic scoring system (SLiDe scoring system) was derived that assigned a linear score (0/1/2/3) to these three covariates. This SLiDe scoring system was statistically a better model for predicting outcome in the present study population than the Cancer of the Liver Italian Program (CLIP) and the Japan Integrated Staging (JIS) scoring systems, as judged by the Akaike Information Criteria.

CONCLUSION: The SLiDe scoring system is useful for the assessment of the prognosis of patients with HCC as long as the Japanese staging system is used, although this uses parameters such as the indocyanine green retention test and DCP, which are not examined routinely in every part of the world. Therefore, the proposed classification should be further validated in other large study populations.

Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake

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Mastrangelo G, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G, Marchi T, Buda A, Pinzani M, Martines D.

Hepatocellular carcinoma (HCC) and liver cirrhosis (LC) are not well-established vinyl chloride monomer (VCM)-induced diseases. Our aim was to appraise the role of VCM, alcohol intake, and viral hepatitis infection, and their interactions, in the etiology of HCC and LC. Thirteen cases of HCC and 40 cases of LC were separately compared with 139 referents without chronic liver diseases or cancer in a case-referent study nested in a cohort of 1,658 VCM workers. The odds ratios (ORs) and the 95% confidence intervals (CIs) were estimated by common methods and by fitting models of logistic regression. We used Rothman's synergy index (S) to evaluate interactions. By holding the confounding factors

constant at logistic regression analysis, each extra increase of 1,000 ppm times years of VCM cumulative exposure was found to increase the risk of HCC by 71%(OR = 1.71; 95% CI, 1.28-2.44) and the risk of LC by 37% (OR = 1.37; 95% CI, 1.13-1.69). The joint effect of VCM exposure above 2,500 ppm times years and alcohol intake above 60 g/day resulted in ORs of 409 (95% CI, 19.6-8,553) for HCC and 752 (95% CI, 55.3-10,248) for LC; both S indexes suggested a synergistic effect. The joint effect of VCM exposure above 2,500 ppm times years and viral hepatitis infection was 210 (95% CI, 7.13-6,203) for HCC and 80.5 (95% CI, 3.67-1,763) for LC; both S indexes suggested an additive effect. In conclusion, according to our findings, VCM exposure appears to be an independent risk factor for HCC and LC interacting synergistically with alcohol consumption and additively with viral hepatitis infection. Key words: alcohol, case-referent studies, cirrhosis, hepatocellular carcinoma, occupational diseases, vinyl chloride.

The impact of immigration on the increasing incidence of hepatocellular carcinoma in the United States

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K. Kulkarni, E. Barcak, H. El-Serag, R. Goodgame

AIMS: To assess if the rising incidence of hepatocellular carcinoma in the United States can be accounted for by immigration and an ageing population, or is a true increase among the USA-born residents.

METHODS: Design- A retrospective chart review. Setting- Urban, multiethnic hospital and specialty clinics in a large indigent health system in Houston, Texas. Subjects- Approximately 23 000 admissions and 143 000 out-patient clinic visits each year from 1992 through 2001 were assessed. A total of 494 patient records were selected and reviewed because of suspicion of hepatocellular carcinoma. Analysis- Hepatocellular carcinoma was confirmed by histopathology, alfa-fetoprotein level >400 ng/mL, and suggestive imaging studies. The age-adjusted incidence was determined and causative factors were identified.

RESULTS: About 111 cases of confirmed hepatocellular carcinoma were found. The age-adjusted incidence rose from 3.44 per 100 000 hospital admissions during 1992-1996 (95% confidence interval: 2.86-4.02) to 5.19 during 1997-2001 (95% confidence interval: 4.41-5.97). The proportion of patients of non-USA place of birth decreased between 1992-1996 and 1997-2001 (46-24%, respectively, P= 0.03). Fifty-two per cent and 68% were hepatitis C virus-positive respectively; 37% and 34% were hepatitis B surface antigen-positive respectively; 46% and 59% had a history of alcohol abuse; and 22% and 11% had no identifiable risk factors.

CONCLUSIONS: The incidence of hepatocellular carcinoma within the greater Houston area has increased during the past decade, rising by 51% from 1992-1996 to 1997-2001. This increase is not from immigration or population ageing but represents a true rise among the native born population. Hepatitis C and alcoholic cirrhosis are associated with a majority of cases, particularly in the latter half of the decade.

The hepatotoxicity of non-steroidal anti-inflammatory drugs

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J. H. Rubenstein , L. Laine

BACKGROUND: Non-steroidal anti-inflammatory drugs have been implicated in reports of liver injury. However, the precise risk of non-steroidal anti-inflammatory drugs for this rare complication is unknown.

AIM: To review systematically the published literature of population-based epidemiological studies reporting the incidence or comparative risk of non-steroidal anti-inflammatory drugs for liver injury resulting in clinically significant events, defined as hospitalization or death.

DATA EXTRACTION: Duplicate extraction of the methodological quality, design, source, population, years studied, particular non-steroidal anti-inflammatory drugs studied, definitions, patient counts and follow-up, and the adjustment for confounders.

RESULTS: Seven articles met inclusion criteria. The comparative risk of liver injury resulting in hospitalization for current non-steroidal anti-inflammatory drug users compared with past non-steroidal anti-inflammatory drug users ranged from 1.2 to 1.7, but none was statistically significant. The incidence of liver injury resulting in hospitalization ranged from 3.1 to 23.4/100Ê000Êpatient-years of current use of non-steroidal anti-inflammatory drugs,

with an excess risk compared with past non-steroidal anti-inflammatory drugs users of 4.8-8.6/100 000 patient-years of exposure. There were zero deaths from liver injury associated with non-steroidal anti-inflammatory drugs use in over 396 392 patient-years of cumulative exposure.

CONCLUSION: These findings allow for the possibility of a small increase in the risk of clinically relevant hepatotoxicity with non-steroidal anti-inflammatory drugs use, but do not document that such a risk occurs.

Visual side effects of pegylated interferon during therapy for chronic hepatitis C infection

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Willson RA.

Ocular toxicity, including retinopathy, optic neuropathy and ocular loss, has been infrequently (<1%) reported as a potentially serious adverse event associated with standard interferon therapy. The new pegylated interferons have improved pharmacokinetics which translates to better antiviral efficacy, however, this improved pharmacokinetic profile also has the potential to alter the frequency and extent of their adverse events. We describe a case of chronic hepatitis C infection that developed visual complaints after one month of pegylated interferon, and retinopathy confirmed on ophthalmologic examination. We place our report in context with a review of the literature related to visual complications associated with interferon therapy. From our compilation of case reports, it is apparent that variable doses and duration of interferon therapy have been associated with ocular toxicity, which in turn suggests an idiosyncratic drug reaction. In as much as this adverse event is unpredictable, and its frequency undefined with pegylated interferon therapy, further surveillance will be required for patients undergoing pegylated-interferon therapy. Although ocular toxicity is uncommon, it should be emphasized that it can occur any time after the start of interferon therapy, and physicians now treating chronic hepatitis C patients with pegylated interferon must be aware of this potentially serious adverse event.

Serious ophthalmic pathology compromising vision in HCV/HIV co-infected patients treated with peginterferon alpha-2b and ribavirin

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Farel C, Suzman DL, McLaughlin M, Campbell C, Koratich C, Masur H, Metcalf JA, Robinson MR, Polis MA, Kottilil S.

OBJECTIVE: To characterize the ocular changes associated with peginterferon alpha 2b (peg-IFN alpha-2b) and ribavirin therapy for chronic hepatitis C infection in HIV co-infected individuals.

METHODS: A prospective, open-label trial treating HIV/hepatitis C (HCV) co-infected individuals with peg-IFN alpha-2b and ribavirin at the Warren Grant Magnusson Clinical Center, National Institutes of Health, Bethesda, Maryland, USA. Twenty-three patients with a high mean CD4+ T-cell count were treated with peg-IFN alpha-2b and ribavirin and followed for 40 to 88 weeks. Ophthalmologic evaluations including visual acuity, visual field testing, color vision examination and indirect ophthalmoscopy were performed at baseline and every 3 months.

RESULTS: Eight of the 23 patients (35%) developed ophthalmologic pathology, including cotton wool spots, cataracts, and two patients developed decreased color vision. These two patients regained their color vision, one after cessation of anti-HCV therapy.

CONCLUSIONS: Although retinal pathologies have been reported in patients treated with interferon-alpha, they have not been reported during peg-IFN alpha-2b therapy nor in HIV/HCV co-infected patients. The incidence of serious ocular pathology associated with anti-HCV therapy may be very high and is probably associated with peg-IFN alpha-2b. Increased monitoring of patients treated with peg-IFN alpha-2b for retinal and visual changes is warranted.

Hepatocellular Lymphoepithelioma-Like Carcinoma Associated with Epstein Barr Virus: A Hitherto Unrecognized Entity

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Si MW, Thorson JA, Lauwers GY, DalCin P, Furman J.

OBJECTIVE: Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma with a dense lymphoid stroma. It has been reported in diverse organs and shows variable association with Epstein-Barr virus (EBV). Only a few EBV positive cases have been observed in the hepatobiliary system, all of which were considered to be cholangiocarcinomas. We report a unique case of hepatocellular LELC arising in a cirrhotic liver with EBV demonstrated in the tumor cells.

METHODS AND RESULTS: A 39-year-old Hispanic female underwent an orthotopic liver transplant for end stage liver disease secondary to chronic hepatitis C. A high-grade hepatocellular carcinoma with a dense lymphocytic infiltrate was found in the explant as well as in a portal lymph node. Three months posttransplant, the patient developed numerous hepatic nodules with enlarged periaortic and portacaval lymph nodes. Biopsy of the hepatic nodules showed a recurrent hepatocellular carcinoma devoid of a dense lymphocytic infiltrate. Both the primary and recurrent tumors were positive for EBV by molecular studies. The patient eventually expired from liver failure over a 6-week period.

CONCLUSION: This case represents the first report of EBV-positive hepatocellular LELC. It is particularly interesting given the precipitous clinical outcome, which was possibly related to immunosuppresive therapy.

Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis

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Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM.

BACKGROUND: There is little information about the effect of infliximab on the clinical course of liver disease in Crohn's disease patients with concomitant hepatitis B virus (HBV) infection. Theoretically, immunosuppression induced by infliximab will facilitate viral replication which could be followed by a flare or exacerbation of disease when therapy is discontinued. There are no specific recommendations on surveillance and treatment of HBV before infliximab infusion. Two cases of severe hepatic failure related to infliximab infusions have been described in patients with rheumatic diseases.

PATIENTS AND METHODS: Hepatitis markers (C and B) and liver function tests were prospectively determined to 80 Crohn's disease patients requiring infliximab infusion in three hospitals in Spain.

RESULTS: Three Crohn's disease patients with chronic HBV infection were identified. Two of the three patients with chronic HBV infection suffered severe reactivation of chronic hepatitis B after withdrawal of infliximab therapy and one died. A third patient, who was treated with lamivudine at the time of infliximab therapy, had no clinical or biochemical worsening of liver disease during or after therapy. From the remaining 80 patients, six received the hepatitis B vaccine. Three patients had antibodies to both hepatitis B surface antigen (anti-HBs) and hepatitis B core protein (anti-HBc) with normal aminotransferase levels, and one patient had positive anti-hepatitis C virus (HCV) antibodies, negative HCV RNA, and normal aminotransferase levels. Except for the patients with chronic HBV infection, no significant changes in hepatic function were detected.

CONCLUSIONS: Patients with Crohn's disease who are candidates for infliximab therapy should be tested for hepatitis B serological markers before treatment and considered for prophylaxis of reactivation using antiviral therapy if positive.