Netherlands
The Journal of Medicine

REVIEW

Malignancies associated with chronic hepatitis C: case report and review of the literature

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ABSTRACT

Hepatocellular carcinoma (HCC) is a well-known consequence of hepatitis C virus (HCV) infection mainly in cirrhotic patients. Associations of other malignancies such as cholangiocellular carcinoma and B-cell malignancies with HCV are less well known. Here we review pathophysiological aspects of malignancies associated with HCV infection. A case report of HCV-related HCC and B-cell lymphoma illustrates the increased risk for HCV-infected patients to develop other malignancies besides HCC.

KEYWORDS

Hepatitis C, lymphoma, cryoglobulinemia, hepatocellular carcinoma, cholangiocellular carcinoma

INTRODUCTION

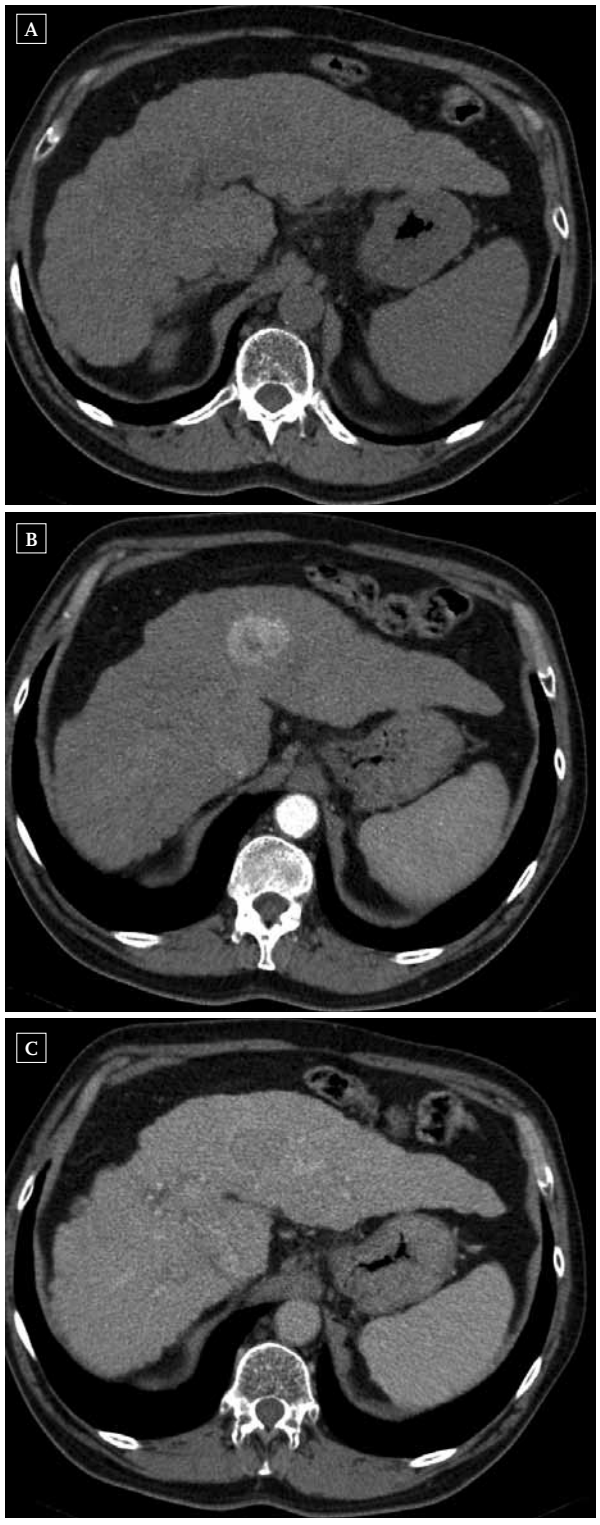
Up to 25% of patients with chronic hepatitis C virus (HCV) infection are known to develop cirrhosis after 25 to 30 years, with a 1 to 4% annual risk to develop hepatocellular carcinoma (HCC).[1] Thus, treatment strategies are directed towards hindering disease progression, hepatic decompensation and development of HCC. There is less awareness of other malignancies associated with HCV infection such as cholangiocellular carcinoma and mixed cryoglobulinaemia (MC) with subsequent progression to B-cell non-Hodgkin's lymphoma (NHL), which may be under-reported and possibly underdiagnosed in HCV-infected patients.[2-4]

HCV infection has been implicated as the major aetiological factor sustaining B-cell clonal expansion in type II MC.[5] Furthermore, it has been speculated that HCV has a pathogenetic role in the development of MC-associated B-cell malignancies.[6] We report on a patient who developed HCC and B-cell lymphoma after successful eradication of HCV. We review the literature on pathophysiological aspects of malignancies associated with HCV infection.

CASE REPORT

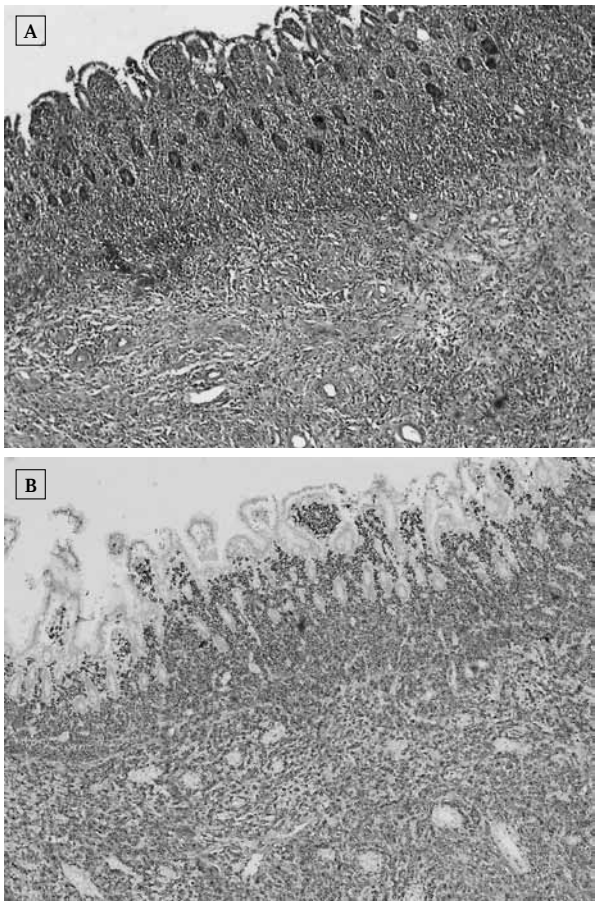
A 73-year-old man presented at our emergency department with severe abdominal pain and shock. The patient was known with Child-Pugh A cirrhosis associated with HCV infection, genotype 2, which was successfully eradicated two years before with peginterferon and ribavirin. Further history of this patient revealed diabetes mellitus type 2, cholelithiasis and prepyloric ulcers. During routine screening of the cirrhotic liver two lesions had been identified in liver segment IV which fulfilled the criteria for hepatocellular carcinoma (HCC) when dynamic imaging techniques were applied *(figure 1)*. The serum alpha-fetoprotein was not elevated. The patient had undergone transarterial chemoembolisation (TACE) of the tumours with doxorubicin and microbeads three months before admission. Additional radio frequency ablation (RFA) was planned because of residual tumour tissue after TACE treatment. However, due to myocardial ischaemia during the last admission, the patient had been discharged to a nursing home to fully recover before performing RFA. Laboratory investigation showed a haemoglobin level of 6.0 mmol/l, mean corpuscular volume of 82.7 fl, platelet count of 246 x 10^9/l, leukocyte count of 10.4 x 10^9/l, a monoclonal paraprotein (positive M-protein with IgA 4.81 g/l, IgG 16.0 g/l and IgM 0.8 g/l), and an elevated lactic dehydrogenase (>1000 U/l) in the last three months. No signs of vasculitis were described by the treating physician. On presentation at our emergency department, ascites analysis disclosed a high leukocyte count and infection

Figure 1. *Hepatocellular carcinoma as indicated by dynamic CT scan in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



The protocol for investigating the presence of hepatocellular carcinoma includes infusion of an intravenous contrast agent and subsequent three-phase scanning: (a) before contrast administration, (b) immediately after contrast administration, and (c) after a delay of four minutes. The three images show the typical pattern of a hepatocellular carcinoma with (b) arterial hypervascularisation immediately after contrast administration, and (c) washout of contrast in one of the delayed phase studies.

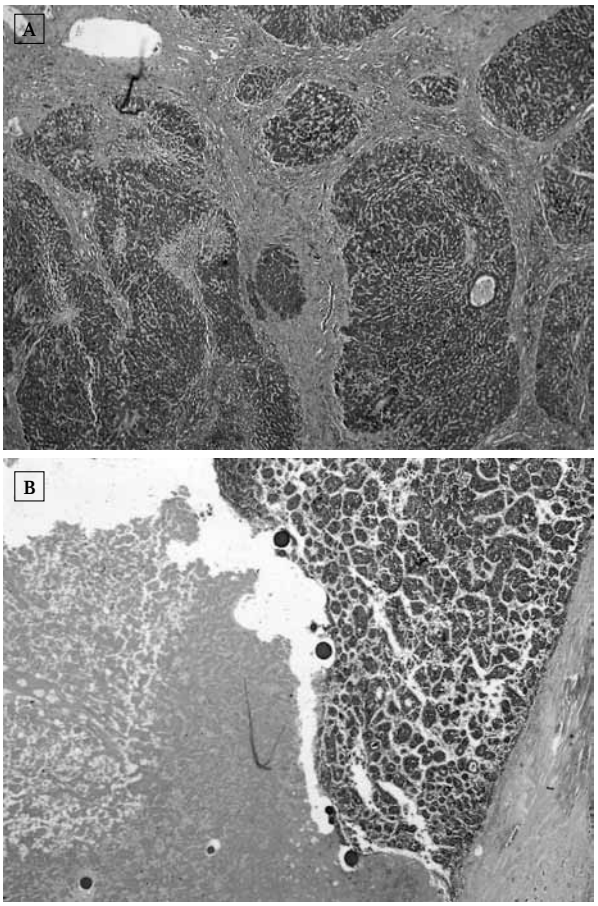
Figure 2. *Large B-cell lymphoma in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



(a) The small bowel wall after resection shows a diffuse infiltrate of large atypical lymphoid cells: haematoxylin and eosin staining (40x). (b) CD20 immunohistochemical staining (40x) demonstrates the B-cell origin of these cells consistent with a large B-cell lymphoma, best classifiable as diffuse large B-cell lymphoma (WHO 4th edition, 2008).

with Gram negative and positive bacteria. CT abdomen was suggestive for intestinal perforation, and lesions suggestive of malignancy were seen in the intestinal wall. Emergency laparotomy confirmed perforation of the small intestine. Resection of the affected intestine and a temporary ileostomy were performed. Pathological examination revealed intestinal large B-cell lymphoma, best classifiable as diffuse large B-cell lymphoma or short diffuse large B-cell lymphoma *(figures 2a* and *b)*. Additional analysis revealed a BCL-6 translocation in the lymphoma but no BCL-2 or c-myc translocation. The patient did not recover and died 15 days after surgery due to multiorgan failure. Autopsy revealed that the B-cell lymphoma was located in the stomach, small intestine, and in the soft tissue around the adrenal gland, but not in the bone marrow or the lymph nodes. HCC was confirmed in the cirrhotic liver *(figures 3a* and *b)*.

Figure 3. *Residual hepatocellular carcinoma after transarterial chemoembolisation in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



(a) Liver tissue after autopsy (20x) shows severe cirrhosis. (b) Largely necrotic tumour tissue after transarterial chemoembolisation with a small rim of vital hepatocellular carcinoma (40 x, haematoxylin and eosin staining).

REVIEW

Hepatocellular carcinoma and hepatitis C

The risk of developing HCC is 1 to 4% per year for a patient with HCV-related cirrhosis.[7,8] Prevalence of HCV in the general population in the Netherlands is estimated at 0.2 to 0.4%.[9,10] Intravenous drug use, tattooing, and medical procedures such as dialysis and blood transfusion before the era of HCV screening have all contributed to the wide spread of HCV. The delay between HCV infection and HCC development between 10 and 30 years raises the expectation that the number of cases with HCV-related HCC will further rise remarkably during the next decade in Europe,[11] as can be seen in the United States of America.[12] The molecular biological pathways leading to HCC development need to be further unravelled in order to intervene early to prevent HCC development and to treat patients more effectively. The contribution to HCC development of HCV-specific viral characteristics and an individual's specific immune response against HCV infection are interesting lines of investigation.

The current understanding of the pathogenesis of HCC in HCV-infected patients is that continuous hepatic inflammation due to a poor clearance of the virus is a major culprit. The poor clearance is due to an error-prone viral polymerase causing high rates of mutants. At present, a shortage of effective and well-tolerable treatment options still leads to treatment failure in a high number of patients. In addition, difficult-to-treat genotypes represent evolution of interferon resilient viruses.[13] Continuous inflammation results in oxidative cell damage and increased cell turnover, which will induce DNA damage, stimulating carcinogenesis and increasing the risk for development of HCC.[14] In line with this, continuously enhanced hepatocyte turnover due to alcohol exposure, steatohepatitis, autoimmune hepatitis, alpha-1-antitrypsin deficiency, haemochromatosis, or Gaucher's disease, can all result in development of HCC.[15-20] Furthermore, as in various other chronic liver diseases, prevention of cirrhosis in HCV-infected patients, even without viral clearance or normalisation of liver enzymes, lowers the risk of HCC development and improves long-term prognosis.[21,22]

HCC is the most common malignancy associated with HCV infection. However, HCV infection is also associated with two other malignancies which deserve attention.

Cholangiocellular carcinoma and hepatitis C

Cholangiocellular carcinoma is the second most common primary hepatic tumour after HCC.[23] Cholangiocellular carcinomas make up 15% of primary liver cancer worldwide. The incidence is estimated to be 1 to 2 cases per 100,000 population in the US.[24] Primary sclerosing cholangitis is one of the most commonly recognised risk factors for cholangiocellular carcinoma.[25] Cholangiocellular carcinomas are highly fatal tumours, as they are clinically silent until a very late stage in the majority of cases.

Cholangiocellular carcinomas, primarily cancers of the epithelial cells in the bile ducts arising anywhere along the intrahepatic or extrahepatic biliary tree, are relatively rare but high incidence rates have been reported in Eastern Asia, especially in Thailand. An explanation for this epidemiological finding is the association of infection with liver flukes (a kind of parasite) of the type *Optisthorchis viverrini* and possibly *Clonorchis sinensis* and the onset of cholangiocarcinoma of the intrahepatic bile ducts.[26] Liver flukes are common in South-Eastern Asia (particularly Thailand) inhabiting and laying eggs in the biliary system

inducing a chronic inflammatory state, presumably leading to malignant transformation of the lining epithelium.

The overriding link between most known risk factors and cholangiocellular carcinoma is chronic inflammation and chronic biliary irritation. From this point of view it has been suggested that HCV may also be a risk factor for the onset of cholangiocellular carcinoma. Indeed, recent studies provide convincing evidence that HCV infection is associated with the onset of cholangiocellular carcinoma. In patients with HCV infection the risk for onset of cholangiocellular carcinoma is increased (relative risk 2.6 (95% CI 1.5 to 4.6)).[23] The role of HCV in onset and pathogenesis of cholangiocellular carcinoma needs further investigation. Recent studies show that the HCV-core protein is significantly associated with cholangiocellular carcinoma invasion and metastasis.[27] The HCV-core protein can alter cellular proliferation and apoptosis in hilar cholangiocarcinoma cells. Because cholangiocellular carcinoma and hepatocellular carcinoma may arise from the same progenitor cells, common mechanisms may in part account for the malignant transformation.[28]

Non-Hodgkin's lymphoma and hepatitis C

There is a body of evidence indicating that infections play a role in the development of lymphomas as evidenced by the association of Ebstein-Barr virus infection with diffuse large cell B-NHL or *H. pylori* infection with mucosa-associated lymphoid tissue (MALT) lymphomas.[29,30] An association between HCV infection and lymphoproliferative disorders, such as MC or lymphoma has been reported by epidemiological studies recently published.[31,32] Between 50 and 90% of patients with MC (consisting of monoclonal immunoglobulins (Ig's), mostly IgM, combined with polyclonal Ig's with rheumatoid factor (RF) activity) have HCV infection; however, only 5% of patients with MC type 2 develop an overt B-cell malignancy.[33,34] In contrast, 5% of patients suffering from a B-cell NHL have evidence of HCV infection.[35] The relative risk for patients infected with HCV to develop B-cell NHL is increased showing a world wide geographic variation with the highest risk in southern Europe (relative risk 2.7).[36] HCV infections are commonly associated with diffuse marginal zone, follicular, large B-cell, and MALT lymphomas without any predilection for the HCV genotype.[37,38] In contrast, HCV-associated monoclonal gammopathy is more often seen in patients infected with either genotype 2a or 2b, respectively.[39]

The pathogenesis of HCV-induced lymphoproliferative disease is not entirely clear yet. Being a positive single-stranded RNA virus lacking a reverse transcriptase, it cannot cause direct insertional oncogenesis.[40] A leading concept suggests chronic antigenic stimulation leading to oligo- and monoclonal expansion of B-cells. In this concept, chronic HCV infection leads to an antigen-specific polyclonal B-cell proliferation. When the antigen is still present, partially transformed B-cell clones are further expanded leading first to oligoclonal and later to monoclonal B-cell proliferation as clinically evidenced by the presence of MC type III (polyclonal Ig's with RF activity) and MC type II, respectively.[40] Finally antigen-independent expansion leads to uncontrolled proliferation becoming apparent as B-cell lymphoma. The hypothesis is supported by the clinical finding that a significant decrease in the viral load by antiviral therapy results in a high percentage of complete response in both MC and B-cell lymphoma.[41,42] The variable regions of the Ig's in patients suffering from HCV infection with MC are hypermutated and the antibodies from different patients are related, as evidenced by variable (V_H)-gene restriction.[40] One of the antigens suspected to induce B-cell proliferation is HCV envelope protein E2. Since E2 can bind to CD81 on B cells, it may in complex with CD19 and CD22 provide strong co-stimulatory signals to support B-cell receptor activation. In addition, binding of E2 to CD81 induces double strand DNA breaks and hypermutations.[40] Besides chronic antigen stimulation, regulatory dysfunction of B cells, such as upregulation of FAS or overexpression of B-lymphocyte stimulator (BLyS), an important survival signal that may also serve as a co-stimulatory proliferation signal, may propagate B-cell expansion as well. Interestingly, patients with chronic HCV infection show a high rate of BCL-2 translocations and overexpression. In addition, patients with HCV infection with MC have a higher rate of BCL-2 expression as compared with HCV-infected patients without MC. However, it is important to realise that patients suffering from HCV infection can directly develop B-cell NHL without evidence of MC.[40] The above-presented concept of HCV-induced lymphoma may also hold true for hepatitis B as recent studies show that besides HCV, hepatitis B is also associated with the onset of lymphomas.[43,44]

CONCLUSION

Patients with chronic hepatitis C virus infection have an increased risk for development of at least three types of malignant disorders, in part probably due to the virus-induced stimulation of the immune system, inflammation and oxidative stress. Physicians should be aware of the HCV-associated onset of B-cell non-Hodgkin's lymphoma and cholangiocellular carcinoma besides hepatocellular carcinoma. This awareness is especially needed for detection of lymphoma when patients have mixed HCV-associated cryoglobulinaemia and incomprehensibly high LDH serum levels as illustrated by the case presented.

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