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BRIEF ARTICLES

Hepatocellular carcinoma in patients with autoimmune hepatitis

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Abstract

AIM: To evaluate and confirm the low incidence of hepatocellular carcinoma (HCC) in patients with autoimmune hepatitis (AIH). At present only very few cases of HCC in patients with AIH and definite exclusion of chronic viral hepatitis have been published, suggesting that HCC due to AIH is rare.

METHODS: In order to further investigate the incidence of HCC in patients with AIH, we reviewed our large cohort of 278 patients with AIH.

RESULTS: Eighty-nine patients (32%) were diagnosed with liver cirrhosis, a preneoplastic condition for HCC. We studied a total of 431 patient years of cirrhosis in these patients, an average 4.8 years per patient. During this period none of the patients of our own study cohort developed HCC. However, three patients with HCC due to AIH associated liver cirrhosis were referred to our department for further treatment of HCC. In all three patients chronic viral hepatitis was excluded.

CONCLUSION: We conclude that HCC may under rare circumstances develop due to chronic AIH dependent liver cirrhosis. Compared to other causes of liver cirrhosis such as chronic viral hepatitis, alcohol, or hemochromatosis, the incidence of HCC is significantly lower. Pathophysiological differences between AIH and chronic viral hepatitis responsible for differences in the incidence of HCC are yet to be further characterized and may lead to new therapeutic concepts in prevention and treatment of liver cancer.

Key words: Autoimmune hepatitis; Hepatocellular carcinoma; Hepatic C virus; Hepatic B virus; Liver cirrhosis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common malignancies world wide and its incidence is rising, especially in Asia and Sub-Saharan Africa, but also in Western countries[1,2]. Most HCCs develop on the basis of liver cirrhosis due to chronic liver disease, making it a prerequisite for development of the disease. HCCs in non-cirrhotic livers are rare and mostly due to aflatoxin B or hepatitis B. Although HCC may develop as a consequence of all entities of underlying liver disease, it has been noticed before that the incidence of primary liver cancer varies significantly between different forms of chronic liver disease leading to cirrhosis and subsequent liver cancer. In hepatitis C patients suffering from liver cirrhosis, the average yearly incidence of HCC has been published as being approximately 1%-4% in Western countries[3-6]. An even higher rate of up to 8% was reported in Asia[1]. Similarly, the corresponding cumulative incidence rates of HCC in patients with chronic

viral hepatitis B were 1.3% and 14.9% per person-year, respectively, depending on HBV DNA levels[7,8]. The risk for HCC in decompensated alcohol-induced cirrhosis approaches 1% per year[9] and was demonstrated to be less in patients without co-infection of chronic viral hepatitis. Furthermore, the rate for HCC developing on the basis of hemochromatosis was reported between 2% and 6% per patient year[10,11]. Finally, HCC due to late stage primary biliary cirrhosis (PBC) was also reported as up to 2% per patient year in late stage (stage IV) PBC[12,13].

For patients with liver cirrhosis due to autoimmune hepatitis (AIH), only very few patients with HCC have been reported, mostly as single case reports. In addition, since in most earlier studies hepatic C virus (HCV) co-infection was not excluded, only very few data exist on the incidence and occurrence of HCC solely on the basis of AIH and subsequent liver cirrhosis[14,15] (Table 1).

However, confirmation of a low incidence of HCC in patients with AIH would point towards a (patho-) physiological mechanism in patients, preventing a much higher incidence as compared to patients with chronic viral hepatitis C. Further characterization of this phenomenon and patient collectives with HCC due to AIH may subsequently lead to identification of protective mechanisms against liver cancer and open new therapeutic perspectives.

Table 1 Summary of the incidence of HCC in patients with liver cirrhosis due to different underlying diseases. Incidence of HCC was demonstrated to be by far the lowest in autoimmune hepatitis

Patients with liver cirrhosis		
Underlying disease	**HCC incidence per year (%)**	**Reference**
Chronic hepatitis C	1-8	[1,3-6]
Chronic hepatitis B	1-15	[7,8]
Alcoholic liver disease	1	[9]
Hemochromatosis	2-6	[10]
Primary biliary cirrhosis (PBC)	2	[12,13]
Autoimmune hepatitis	< 0.2	

MATERIALS AND METHODS

Study cohort

Two hundred seventy-eight patients satisfied the international criteria for the diagnosis of AIH[16]. They had been enrolled in our chronic liver disease program from 1970 until present and were reviewed for evidence of HCC. All patients had been followed in a uniform fashion for a total of 1951 years (0-34 years). On the basis of immunoserological assessment for autoantibodies, 207 patients were assessable for subtypes of AIH. Of these 195 patients (94%) were classified as type-1 AIH due to positive ANA, SMA, or anti-SLA/LP autoantibodies[17,18]. Eleven (6%) patients had elevated LKM autoantibodies, characteristic for type Ⅱ AIH[19]. Seventy-two patients had no detectable autoantibodies. Follow-up was usually maintained at three-month or six-month intervals during treatment discontinuation and for at least one year after treatment. Thereafter, follow-up assessments were performed at annual intervals, if the clinical condition was stable. Hepatic ultrasound and serum α-fetoprotein determinations were usually repeated every 6-12 mo. Follow up on patients with diagnosed liver cirrhosis was documented for 431 patient years. Follow up on patients not suffering from liver cirrhosis accumulated to 1183 patient years. The diagnosis of HCC required histological documentation.

Immunoserological assessments

SMA, ANA, and LKM were analyzed by indirect immunofluorescence on murine tissue sections as described previously. Anti-SLA/LP were analyzed by inhibition ELISA[18]. A serum titer of 1:80 or higher was considered positive for ANA[17]. A titer of 1:40 or higher was considered positive for SMA. A titer of 1:40 or higher was considered positive for anti-LKM-1[19]. All patients were tested for SMA and ANA, and 193 patients (91%) were tested for anti-LKM-1. Patients with SMA and/or ANA in the absence of anti-LKM-1 were classified as type-1 AIH. Patients with anti-LKM1 were classified as type-2 AIH[19].

Virological assessments

Antibodies to anti-HCV were detected by a second-generation enzyme linked immunosorbent assay (ELISA) and HCV RNA was assessed in serum by PCR. Hepatitis B surface antigen (HBsAg) was determined by ELISA.

HCC patient 1

A 59-year-old male presented at our institution with hydrops decompensated cirrhosis (Child-Pugh Score C) and suspected HCC due to previously diagnosed AIH (SMA positive, anti-SLA/LP positive) and overlap syndrome to primary biliary cirrhosis. The patient had previously been treated at an external hospital over 25 years for cryptogenic hepatitis. Through the course of disease, the patient had been intermittently treated with prednisolone, and at presentation at our department treatment consisted of prednisolone 15 mg/d. For 5 years prior to his presentation at our department, the patient had intermittently been treated with lactulose, pointing to presence of decompensated liver cirrhosis and thus, retrospectively, liver cirrhosis must be assumed to have existed several years prior to presentation. Esophageal varices were known at least 2 years prior to presentation at our department. An accompanying chronic viral hepatitis was excluded by means of serological testing.

After presentation at our department a large liver tumor measuring 9.8 cm × 8 cm × 7.5 cm was found by ultrasound and CT scan. Histology confirmed the diagnosis of HCC. Due to the lack of surgical options, the patient underwent transarterial chemoembolization as palliative treatment. Initially, the intervention was performed without complications and the patient was released from the hospital in good condition. However, three weeks later, the patient was re-admitted to our emergency department with abdominal pain and signs

of subileus. Splenic rupture was identified. The patient died the following day.

HCC patient 2

A 78-year-old female was admitted to our hospital with a confirmed longstanding course of AIH under immunosuppressive therapy. ANA and SMA autoantibodies were positive with high titers. Liver cirrhosis (Child-Pugh-Score A) had previously been diagnosed. Initial diagnosis of AIH was made 12 years prior to presentation at our department and the patient was treated with an immunosuppressive regimen. At presentation at our department medication consisted of prednisolone 2.5 mg/d and azathioprine 100 mg/d. An accompanying chronic viral hepatitis was excluded by means of serological testing. Shortly after presentation, HCC was diagnosed by means of ultrasound and CT scan in addition to elevated tumour marker AFP (1000 ng/mL). The patient declined all therapeutic options and decided for best supportive care near her hometown. Thus, no follow up on the patient's condition or course of HCC was available.

HCC patient 3

A 46-year-old female was admitted to our department for histologically confirmed HCC and liver cirrhosis (Child-Pugh-Score C) due to AIH. Sixteen years prior to presentation, the patient had already been treated for "non-A/non-B" hepatitis. Thus, retrospectively, a longer course of AIH must be assumed. Throughout the course of disease, treatment had been extended to prednisolone and azathioprine. An accompanying chronic viral hepatitis was excluded by means of serological testing. A CT scan demonstrated two nodes of 8.8 cm × 7.7 cm and 2.3 cm × 1.8 cm, confirmed to be HCC. Due to tumour size and lack of sufficient size of the potentially remaining liver after surgical resection, surgery was declined and the patient was offered palliative chemotherapy. However, the patient declined chemotherapeutic treatment and was lost in follow up.

RESULTS

In order to investigate the incidence of HCC in patients with AIH, we retrospectively examined our large cohort of 278 patients with AIH. Twenty-nine patients (10%) had been under treatment for AIH for less than one year. Thirty-two patients in the study cohort (11%) had cirrhosis at presentation. Of the remaining 255 patients, fifty-seven (22%) developed cirrhosis despite treatment at our department. Together, the total number of patients with cirrhosis and thus at risk for developing HCC was 89 (32%).

For these patients, a total of 431 patient-cirrhosis-years were evaluated. Median follow up time in patients with cirrhosis was 4.8 years (58 mo). Twenty-seven of these patients had a follow up with cirrhosis of more than five years. Overall, these patients were observed for an average of 8.6 years. Twenty-nine patients (10%) were under treatment for less than one year. During this period, none of the 278 patients developed HCC. Three more patients with HCC on the basis of liver cirrhosis due to AIH were referred to our department for treatment of HCC. However, the HCC did not develop during treatment or follow up within our study group. None of those patients seen for HCC in cirrhosis due to AIH tested positive for HCV or HBV or showed any signs of other chronic liver disease. Thus, these patients were excluded from our cohort for calculation of the incidence of HCC per patient-cirrhosis-years.

The 189 patients not developing liver cirrhosis during follow up were observed for a total of 1183 patient years, an average of 6.3 years. None of these 189 patients lacking histological evidence of cirrhosis developed HCC during the time of observation.

DISCUSSION

HCC is among the most common cancers worldwide and its incidence is rising. However, the incidence of HCC in patients with liver cirrhosis varies due to the underlying chronic liver disease. The risk of developing HCC due to chronic hepatitis was estimated to be approximately 1%-8% per patient year in patients with Hepatitis C[4-6,20,21] and 1%-15% in patients with hepatitis B[8]. Incidence in patients with alcoholic liver disease or hemochromatosis was reported to be somewhat lower, but still at the lower margin of the risk of patients with chronic viral hepatitis[9-11]. Finally, HCC incidence due to late stage primary biliary cirrhosis (PBC) was also reported to be up to 2% per patient year in late stage (stage Ⅳ) PBC[12,13].

Contrary to the number of reports on patients with chronic viral hepatitis, only very few cases of patients with HCC developing due to AIH have been reported. Furthermore, most of these patient reports were published before the era of HCV screening and thus, many of these may be accounted for by a HCV co-pathogenesis[15]. At present, besides individual case reports, only a single larger patient cohort has been published, definitely excluding HCV co-pathogenesis[14]. Park *et al*[14] demonstrated a low incidence of HCC in patients with AIH and cirrhosis. They observed only one HCC in 88 patients with cirrhosis due to AIH and in a total of 212 patients, pointing towards an incidence of HCC in patients with liver cirrhosis of about 0.1%. Comparing these numbers to patients with cirrhosis due to chronic viral hepatitis, a significant difference in the occurrence of HCC in cirrhotic livers due to these different entities becomes obvious.

In our cohort of 278 patients with AIH, 89 (32%) patients suffered from liver cirrhosis. During the period of follow up, none of the patients of our own cohort developed HCC. Three more patients with HCC on the basis of cirrhosis due to AIH were referred to our department for treatment of HCC (tertiary referral center for treatment of HCC). However, these patients were referred to our department already with the definite diagnosis of HCC or suspected liver cancer and reason for referral was treatment for HCC. Thus, the existence

of these three patients further confirmed the potential occurrence of HCC in patients with AIH-associated liver cirrhosis. Nevertheless, the patients were not included for the calculation of the incidence of HCC per patient-cirrhosis-years. Therefore, incidence of HCC in patients with cirrhosis due to AIH must be estimated to be less than 0.2% per patient-cirrhosis-year, since HCC was not observed in our cohort in 431 patient years.

Most importantly, all three patients seen for HCC in cirrhosis due to AIH tested negative for HCV or HBV. In two patients no signs of chronic liver disease other than AIH were diagnosed. However, patient 1 was known to suffer from overlap to PBC. Thus, we confirmed that development of HCC may occur independently of co-infection with any form of chronic viral hepatitis or other common causes for liver cirrhosis.

Our results were in accordance with the results published by Park *et al*[14], which primarily demonstrated a significantly lower incidence of HCC in patients with AIH. Although our total patient number was larger than the Park study[14], we had comparable numbers of cirrhosis in our patients, i.e. 89. These patients were observed for a total of 431 years. Median follow up was 4.8 years, which was less than the Park study. Since to our knowledge, the study by Park *et al*[14] still remains the only data on a comparably large cohort, evidence for an altered pathomechanism for HCC development in cirrhosis due to AIH must be considered.

Although the pathogenesis behind this significant difference in HCC development remains to be further elucidated, it may hold important insight into the pathomechanism of HCC differentiation. The lower incidence of HCC in AIH patients is even more surprising since AIH patients are commonly treated with immunosupressants such as steroids and azathioprine, potentially increasing the risk of malignant transformation. However, immunosuppressants such as steroids act through suppressing cytokines, important for inflammation. An increased production of some these cytokines, IL-1β and TNF-α, have been demonstrated to coincide with the presence of liver cancer[22]. Thus, downregulation of these cytokines by immunosuppressive therapy[23,24] may be speculated to contribute to protection from the development of HCC.

In conclusion, we characterized our large collective of patients with AIH and were able to demonstrate and confirm a low incidence of HCC in these patients. The further characterization of patients with HCC due to autoimmune hepatitis may finally lead to the identification of new therapeutic targets preventing the development of liver cancer and thus novel therapeutic strategies.

COMMENTS

Background

At present only very few cases of hepatocellular carcinoma (HCC) in patients with autoimmune hepatitis (AIH) and definite exclusion of chronic viral hepatitis have been published, suggesting that HCC due to AIH is rare.

Research frontiers

Compared to other causes of liver cirrhosis such as chronic viral hepatitis, alcohol, or hemochromatosis, the incidence of HCC due to AIH is significantly lower. From our data it was estimated to be less than 0.2% per patient-cirrhosis-year.

Innovations and breakthroughs

This study confirms that AIH patients have a lower risk of HCC than patients with other chronic liver disease, despite their often long term treatment with immunosuppressants.

Applications

Immunosuppressants such as steroids act through suppressing cytokines, essential mediators in inflammation. An increased production of some of these cytokines, IL-1β and TNF-α, has been demonstrated to coincide with the presence of liver cancer. Thus, downregulation of these cytokines by immunosuppressive therapy may be speculated to contribute to protection from the development of HCC. Identifying the differences in patients with AIH and other chronic liver diseases may lead to the identification of protective mechanisms against liver cancer.

Peer review

Compared to other causes of liver cirrhosis such as chronic viral hepatitis, alcohol, or hemochromatosis, the incidence of HCC due to AIH is significantly lower. From our data it was estimated to be less than 0.2% per patient-cirrhosis-year. This study confirms that AIH patients have a lower risk of HCC than patients with other chronic liver disease, despite their often long term treatment with immunosuppressants.

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