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Hepatocellular Carcinoma in Hemophilia

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A questionnaire-based survey involving 11,801 hemophiliacs from 54 hemophilia centers in the USA and Europe documented the occurrence of hepatocellular carcinoma (HCC) in 10 patients. The crude rate of HCC was 3.2/100,000 patients/year, at least 30 times higher than the background incidence of this tumor in the countries of origin of the patients. All patients were Caucasians with hemophilia A, 39 to 74 years of age, and had liver cirrhosis. All had one or more risk factor for cirrhosis and HCC: 5 were positive for serum hepatitis B surface antigen, 4 had the antibody to hepatitis C virus, and 4 had histories of alcohol abuse. Serum alpha-fetoprotein, measured in 6 patients, was significantly elevated in 4 (range: 807–1399 ng/ml), and only moderately elevated in 2 (25 and 171 ng/ml). The onset of HCC was asymptomatic in 5 patients, whereas it was accompanied by jaundice, abdominal pain, or ascites in the remaining patients. Thus, HCC seems to be a more important secondary disease for hemophiliacs than formerly recognized. Since HCC is often asymptomatic, screening hemophiliacs with chronic liver disease with periodic ultrasound scans might increase the chances of detecting HCC at a stage amenable to surgical treatment.

Key words: hepatitis B, hepatitis C, hemophiliacs

INTRODUCTION

Approximately 50% of multitransfused hemophilic patients have serologic signs of chronic liver disease, and 20% of them show histological signs of cirrhosis [1,2]. The leading causes of cirrhosis are transfusion-associated infections with hepatitis B virus (HBV) and, more importantly, hepatitis C virus (HCV), the agent of parenterally transmitted non-A, non-B hepatitis.

Postmortem reports and prospective cohort studies in non-hemophilic patients with chronic liver disease have provided clear evidence that patients with cirrhosis are at risk of developing HCC [3,4]. Whether this is also true for hemophiliacs is not known. In these patients, the effect of the high prevalence of chronic viral hepatitis and cirrhosis, which predispose to HCC, were long counterbalanced by a decrease in life expectancy [5], which reduced the chances of tumor development. Early autopsy studies in hemophiliacs reported only one case of death attributable to HCC [6–10], and recently two more cases of HCC were reported in living hemophiliacs who also had cirrhosis [11,12]. To obtain more information on the incidence of HCC, we carried out a questionnaire-based survey among large hemophilia centers worldwide.

MATERIALS AND METHODS

In April 1990, eighty-nine centers (46 in the USA and 43 in Europe), all those listed in the directory of the World Federation of Hemophilia, were first contacted to ascertain whether or not they had seen a case of HCC. Centers which gave positive answers were then asked to fill out a more detailed questionnaire. The questionnaire sought data about demography of the patients; alcohol intake (alcohol abuse was considered the daily intake of more than 80 g ethanol); type of hemophilia (factor VIII or factor IX deficiencies) and its severity (severe hemophilia, less than 1% factor; moderate, 1 to 5%; mild, more than 5%); age at onset of HCC; presence of chronic

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liver disease defined either histologically or by the presence of persistently abnormal values of serum aminotransferases; status of serological markers of blood-borne infections, such as serum hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), and antibody to human immunodeficiency virus (anti-HIV). Centers were asked to specify which symptoms or other circumstances led to the diagnosis of HCC; whether or not patients had presented with symptoms suggestive of HCC, such as hepatic mass, abdominal pain, or jaundice; had had deterioration of pre-existing liver disease; had undergone specific screening of HCC by abdominal ultrasound scans and measurement of serum AFP; and whether HCC was found during clinical examination or at autopsy. Centers were also asked to provide information on how the final diagnosis of HCC was established; whether the tumor was a solitary mass or consisted of multiple nodes; and whether or not the patients had extrahepatic secondaries. Additional questions dealt with the treatment for HCC and the actual status of the patient.

RESULTS

Fifty-four of 89 centers (30 in the USA, 24 in Europe) provided information on 11,801 male hemophilic patients (average age: 28 years, range 1–72). Ten cases of HCC were reported from 8 centers (Table I). The crude rate of HCC was 3.2/100,000 patients/year. All patients with HCC were Caucasian males 39 to 74 years of age, and had severe hemophilia A and liver cirrhosis. The HBsAg status was known in 9 patients, anti-HCV in 5, and anti-HIV in 8: five patients had serum HBsAg, four had anti-HCV. One HBsAg seropositive patient also had antibody to hepatitis delta virus (anti-HD) and anti-HCV. One had neither hepatitis marker. Four of 8 tested patients were anti-HIV positive. For 8 patients there was also information on alcohol consumption: 4 had been drinking excess alcohol for more than 5 years. Serum AFP was measured in 6 patients: 4 had AFP levels well above the value of 500 ng/ml (normal value less than 20 ng/ml), which is considered diagnostic for HCC. One had increased levels (171 ng/ml) of AFP below the cut-off value for HCC; another had borderline values (25 ng/ml). Five patients had had symptoms (2 abdominal pain, 2 jaundice, 1 ascites); the remaining patients were asymptomatic. The tumor was multifocal in 7 and unifocal in 3. Seven patients were given no treatment for HCC. One was treated by chemotherapy (cisplatin), one underwent hepatic resection and one orthotopic liver transplantation. Six patients died of HCC. In two, one who died of a ruptured aortic aneurysm and the second of variceal bleeding, HCC was incidentally discovered at autopsy. The remaining two patients, who had undergone orthotopic liver transplantation or hepatic resection, are still alive and tumor-free 32 and 18 months after treatment.

DISCUSSION

HCC seems to be a more important secondary disease in hemophilia than previously recognized. The crude rate of HCC among the hemophiliacs that we surveyed was 3.2/100,000 patients/year, which is at least 30 times higher than the corresponding age-adjusted background incidence of this tumor in the USA, West Germany and Italy (the countries of origin of the patients) [13]. Even if we assume that the centers that did not respond to the questionnaire (about 40% of those surveyed) had seen no cases of HCC, the rate of HCC would still be much higher than in the general population (ca. 20 times higher). There may be several explanations why the importance of HCC in hemophilia has long been overlooked. The frequency of transfusion-associated hepatitis, the most important factor predisposing to HCC in this setting, was relatively low until the 1970s, when commercial clotting factor concentrates were first employed on a large scale and transmitted hepatitis to a high proportion of hemophiliacs [1,2]. Another possible explanation is that before the widespread use of commercial concentrates, the average life-span of hemophiliacs was shorter than 20–30 years, which is thought to be the average incubation period for transfusion-associated HCC [14–16].

A clinically important fact provided by this survey is that all patients with HCC also had cirrhosis. Likely causes of cirrhosis in these patients were hepatitis viruses and alcohol, as indicated by the presence of serum HBsAg and/or anti-HCV in 8 patients, and history of alcohol abuse in four. Several postmortem reports and cohort studies in non-hemophilic patients have provided unequivocal evidence that patients with cirrhosis are at high risk of developing HCC [3,4]. The association between cirrhosis and HCC provides a means to identify patients who are at risk of HCC and therefore require subsequent follow-up. Unfortunately assessment of cirrhosis in hemophilic patients may be difficult. Percutaneous liver biopsy, the hepatologist's gold standard, cannot be performed as a routine, because of the hemorrhagic hazards connected with this procedure. The follow-up of patients with periodic assessments of serum aminotransferases (ALT) might be diagnostically helpful, since hemophiliacs with persistently elevated ALT are at higher risk of cirrhosis than those who have intermittently abnormal or persistently normal ALT values [17,18]. As expected the diagnostic accuracy of serum AFP levels was limited, because AFP was significantly elevated in only 4 of 6 hemophilic patients who had ultrasound scan evidence of HCC. Accordingly, in

TABLE I. Epidemiological and Clinical Characteristics and Outcome of 10 Patients With Hepatocellular Carcinoma*

Case	Center	Patient age (yr)	Serum markers				Liver cirrhosis	Alcohol abuse	Presenting symptoms	Tumor characteristics	Therapy	Present status
			HBsAg	Anti-HCV	Anti-HIV	AFP (ng/ml)						
1	Worcester, MA	74	Pos	NA	Pos	NA	Yes	Yes	None[b]	Diffuse	None	Dead[d]
2	Padua, Italy	46	Pos	NA	Neg	1,060	Yes	NA	Abdominal pain	Multifocal	None	Dead
3	Padua, Italy	51	Pos	NA	Neg	171	Yes	NA	Ascites	Multifocal	None	Dead
4	Miami, FL	56	Neg	Pos	Pos	1,399	Yes	No	Abdominal pain	Unifocal	Cysplatin	Dead
5	Milan, Italy	55	Neg	Pos	Pos	NA	Yes	No	Jaundice	Unifocal	None	Dead
6	Vicenza, Italy	39	Neg	Neg	Neg	25	Yes	Yes	Jaundice	Multifocal	None	Dead[d]
7	Frankfurt, Germany	49	Pos[a]	Pos	Neg	1,200	Yes	Yes	None	Multifocal	OLT[c]	Alive
8	Frankfurt, Germany	52	Neg	Pos	Pos	807	Yes	No	None	Unifocal	Resection	Alive
9	Providence, RI	49	NA[b]	NA	NA	NA	NA	Yes	None	Lung metastases	None	Dead
10	Chapel Hill, NC	42	Pos	NA	NA	NA	Yes	No	None[b]	Multifocal	None	Dead

*NA = information not available.
[a]These patients also had anti-HD.
[b]In these patients HCC was incidentally diagnosed at autopsy.
[c]Orthotopic liver transplantation.
[d]These patients died of causes other than HCC, which was incidentally discovered at autopsy.

order to detect HCC early, hemophiliacs with cirrhosis and those with persistently elevated serum aminotransferases could be screened at least annually by means of ultrasound scanning. Two patients in whom asymptomatic HCC was detected by ultrasound scan are alive and tumor-free several months after hepatic resection or orthotopic liver transplantation.

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