Hepatocellular Carcinoma in a Teenager with Perinatally Acquired HIV Infection without Hepatitis B or C Coinfection: A Case Report

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Abstract

A 19-year-old male with perinatally acquired HIV infection and AIDS (clinical stage 3) presented with a 9.1×5.0 cm hepatic mass. The resected mass was determined to be a hepatocellular carcinoma (HCC) without metastasis. The patient did not have active hepatitis B or C coinfection, as revealed by polymerase chain reaction (PCR), nor other risk factors for development of cirrhosis or HCC, and comprises only the second explicitly stated case of an HIV-positive individual developing HCC in the absence of concomitant hepatitis virus infection or other risk factors. This case illustrates the fact that as survival of perinatally infected individuals increases in the highly active antiretroviral therapy (HAART) era, new associations between HIV infection and other disease processes may be uncovered.

Case Report

IN DECEMBER 2004, a 16-year-old African American male with advanced perinatally acquired HIV infection, AIDS defined (clinical stage C3) and a history of multiple complications (lymphocytic interstitial pneumonia, nephropathy, and hypergammaglobulinemia with humoral deficiency) was discovered incidentally to have a 2×1.4 cm, homogeneously enhancing left-lobe hepatic lesion on chest computed tomography (CT) scan performed for pneumonia-like symptoms. The appearance of the lesion was considered consistent with a hemangioma. Further work-up was not performed until 2009, when at the age of 20 the patient was hospitalized for hemoptysis. CT revealed that the hepatic lesion had grown significantly in the interim period to 8.5×6.0 cm. A magnetic resonance imaging (MRI) revealed a 9.1×5.0 cm peripherally located mass in the left lobe with bulging of the liver contour. The lesion was T1 isointense, moderately T2 hyperintense, with heterogenous arterial and homogeneous portal venous phase enhancement.

Ultrasound-guided fine needle aspiration (FNA) and core biopsy of the lesion was performed in March 2009. FNA and core biopsy revealed a well-differentiated hepatocellular neoplasm with features suggestive of hepatocellular carcinoma.

In April 2009 the patient underwent partial left hepatectomy as well as cholecystectomy. Gross pathologic examination of the resected specimen revealed a well-circumscribed, 8-cm tumor in a noncirrhotic liver. Microscopically, the tumor had a fairly well demarcated margin with a broad pushing border that excluded portal tracts. The tumor contained well-differentiated hepatocytes with several foci of reticulin loss and strong, diffuse CD 34 expression along widened hepatic cords (Fig. 1A and B). The background liver parenchyma showed minimal lymphocytic portal chronic inflammation, no significant steatosis, cholestasis, stainable iron, or fibrosis. No PAS-positive diastase-resistant cytoplasmic granules suggestive of α_1 -antitrypsin deficiency were present. The absence of cholestasis, florid duct lesions, or biliary type of fibrosis was inconsistent with underlying primary biliary cirrhosis. Interface hepatitis with characteristic necrosis and fibrosis, as would be expected with a background of active autoimmune hepatitis, was absent. The surgical margin was clear of the neoplasm; there was no gross or microscopic vascular invasion and no metastatic neoplasm in the hilar and periaortic lymph nodes. The mass was staged at T1N0M0 per American Joint Committee on Cancer (AJCC) criteria.¹ No further treatment was undertaken. The patient is now 14 months removed from surgical resection, with imaging revealing no evidence of recurrence.

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The patient has had a complicated medical history with profound immunodeficiency and multi-drug-resistant viremia due to chronic, suboptimal medication adherence. His medical complications include biopsy-proven lymphoid interstitial pneumonitis, hypertension secondary to nephropathy, and recurrent pneumococcal bacteremia secondary to humoral immune deficiency, necessitating regular administration of intravenous immunoglobulin. Specifically, the patient was diagnosed with hypergammaglobulinemia secondary to HIV/AIDS, which in turn decreased the ability of the humoral defense system to develop specific antibodies to infection or immunization. In addition, decreased complement function was noted with CH50 levels measured at 14 units.

In December, 2004 when the lesion was first explicitly noted on radiographic imaging, his absolute CD4 count was 85 cells/mm³ and HIV-1 RNA levels were 82,616 copies per milliliter. Immediately prior to resection, CD4 count was 18 and HIV-1 RNA was 71,617 copies per milliliter (Fig. 2). Although he has been maintained on highly active antiretroviral therapy (HAART), due to nonadherence, he has never had durable virologic suppression or immunologic recovery.

FIG. 1. (A) Well-differentiated hepatocellular carcinoma (hematoxylin and eosin stain, 20×magnification). (B) Loss of reticulin staining evident in the left half of the photomicrograph (20×magnification).

The patient had negative hepatitis C virus (HCV) antibody screens in 2000, 2002, and most recently in March 2009. He has no HCV risk factors (e.g., injection drug use, known maternal HCV infection, men who have sex with men (MSM) activity, or blood transfusions). HCV RNA testing was negative (<43 or <1.63 log). While he received the complete hepatitis B vaccination (HBV) series, hepatitis B surface antibody (HBsAb) titers measured at less than 3.0 mIU/mL in 2002 and repeat vaccination was performed in 2003–2004. HBV surface antigen was negative in both 2000 and March 2009 and HBV DNA levels were undetectable as assessed by PCR.

Although he has had longstanding hypoalbuminemia (2.4–3.4g/dL), coagulation studies and liver enzymes have consistently been within normal limits, except for a transient elevation in enzymes temporally related to resection. All measurements of iron saturation (from 1994 to March 2009) and serum ferritin levels (2004, 2009) were within or below normal limits (4–30%, 92–179 ng/mL, respectively), as were serum transferrin levels (140–334 mg/dL). Anti nuclear antibody (ANA) and anti-DNA antibody levels were negative as well.

The patient has no history of living or traveling outside the continental United States. He endorses occasional alcohol use, quantified as a few drinks weekly to monthly, since age 16. He reports occasional marijuana use and all drug tests on record have been positive only for marijuana. He denies use of any other illicit drugs, including crystal methamphetamine, non-prescription drugs, or herbal supplements. He denies frequent or high-dose acetaminophen ingestion. There is no history of exposure to other potential hepatotoxins (i.e., aflatoxin).

Discussion

HCC is the most common primary cancer of the liver. One of the leading causes of cancer-related deaths in the United States, HCC's annual incidence has increased by approximately 80% over the past two decades to rates of 2.4 per 100,000 cases in the early 1990s. HCC incidence increases with age and the highest prevalence is seen in individuals above the age of 65.² It is very rare in children and adolescents with an incidence of 0.5 to 1 cases per million.^{3,4}

Cirrhosis of the liver remains the major risk factor for HCC, associated with over 90% of HCC cases in the Western world.¹ Cirrhosis itself is the sequela of various conditions, including viral disease (specifically chronic HBV and HCV infection), toxin exposure, metabolic disorders such as diabetes, and other diseases including hemochromatosis, autoimmune hepatitis and primary biliary cirrhosis.² HCV infection is the most important risk factor for development of HCC in North America and northern European countries, where studies have revealed that nearly 70% of individuals with HCC are anti-HCV antibody positive.² HBV is also an important causal factor in the development of cirrhosis and subsequent HCC development, including among children and adolescents in southeast Asia, where the incidence of HCC is nearly fivefold that of other regions in the world.² Mass HBV vaccination programs in Taiwan, for example, led to a decline in HCC incidence among 6- to 14-year olds from 0.7 to 0.36 per 100,000 children, with a subsequent, time-delayed decrease in incidence among adults as well.²

In recent years, researchers have discovered an increasing incidence of HCC in HIV-infected individuals, thought to

FIG. 2. Absolute CD4 count and viral load (in log scale) from December 2004 to present. Data points from time of initial imaging and resection are indicated with arrows.

reflect in part the success of HAART in lengthening survival, secondarily leading to increased clinical presentation of HCC. One prospective U.S. study revealed a nearly sevenfold difference in incidence of liver cancer in the HIV-positive population in comparison to the general population.⁵ A major component of this difference is attributed to the increased likelihood of HCV and/or HBV coinfection in people living with HIV.^{6,7}

HCC in the absence of HCV or HBV coinfection among HIV-positive patients is exceedingly rare. The first and only explicit case of HCC in an HIV-positive patient without evidence of HCV or HBV infection was reported by Tanaka et al.⁸ in 1996, in a 51-year-old Japanese man with HIV and rapidly progressive HCC with serologies suggestive of past HBV infection (positive HBV surface antibody and core antibody), but no evidence of chronic, persistent HBV or HCV infection. In addition, pathology did not reveal evidence of HBV integration in hepatic tissue, but showed “regenerative nodular formation” of nontumor tissue.⁹ Data from larger scale studies by Giordano et al.¹⁰ and Brau et al.¹¹ indicate that there were only 2 cases of HCC without coinfections with HCV and/or HBV out of a cohort of approximately 11,700 HIV-positive individuals with HCC. However, these two reports do not explicitly deny the existence of other underlying disease or pathology that might explain HCC development. Furthermore, both studies examined incidence in older patients (mean age 44.3 and 52.2 years, respectively). No cases in younger patients or perinatally infected individuals have been reported. Of note, it is also unclear in the two cases whether HCV RNA or HBV DNA analysis was performed to rule out the possibility of serosilent hepatitis infection in those individuals considered noninfected; serosilent HCV in particular has been observed in HIV-positive individuals, thought secondary to abnormal antibody and cellular responses.¹² In our patient, serum PCR analysis did not reveal serosilent HCV or HBV infection.

Our patient’s case is unique in that HCC development occurred at a young age in the absence of HCV or HBV coinfection or other known risk factors (e.g., excessive alcohol exposure, hemochromatosis) and without frank cirrhotic changes. This raises the question of whether HIV may be implicated in the development of HCC in this young, perinatally infected patient with no other risk factors. While retrospective cohort studies examining the relationship between HIV and HCC have not revealed increased HCC incidence in individuals infected only with HIV, other evidence is suggestive of a causal relationship, specifically, mouse models of HIV infection have implicated the HIV *Tat* gene in tumorigenesis in both HCC and other extrahepatic neoplasms.⁶ There is also accumulating evidence for the potential effect of chronic, unchecked inflammation on classically non-HIV-related conditions.⁵ Our patient’s longstanding HIV infection and medication noncompliance with resultant persistent viremia, may have significant implications for chronic inflammation and potentially the development of HCC.

Another element of this case whose significance is less clear, but worthy of discussion, is the limited extent of disease noted upon resection, nearly 5 years after radiologic appearance of the lesion in a chronically immunosuppressed host. Kakizaki et al.¹³ reported a cohort of untreated individuals with HCC (HIV or HCV status not reported) with median survival of 15.2 months from diagnosis to death (most deaths due to HCC-related sequelae and hepatic failure secondary to cirrhosis), suggestive of a relatively rapid timeline for disease progression. It is unclear what contribution uncontrolled HIV and immunosuppression has on this timeline. Brau et al.¹⁰ describe no difference in tumor staging between HIV-positive and -negative patients at time of presentation. However, Puoti et al.¹⁴ in a retrospective study of HCC, report a significant association between HIV infection, multifocal lesions and infiltrating tumors or extranodal metastases upon presentation. Such evidence suggests that HCC may be linked with

parameters measuring severity of HIV/AIDS, and it has been postulated that CD4 and CD8 counts correlate inversely with HCC progression and spread secondary to a weakened anti-tumor immune response.⁹ Also, the relationship between HIV-disease severity and incidence of AIDS-defining malignancies suggest that the former may influence neoplasm development.⁵

Our patient is one of very few cases of HCC observed in an HIV-positive individual without concomitant HCV or HBV infection, evidence of background cirrhotic changes or other notable risk factors. The case is also notable for HCC occurrence in a perinatally infected adolescent presenting with discrete foci of disease without further systemic involvement despite his profoundly immunosuppressed status.

As perinatally infected individuals have increased survival in the HAART era, we may begin to uncover associations between HIV infection and disease processes not yet observed. There needs to be high vigilance for the development of unusual malignancies. Longitudinal cohort studies are essential to defining the prevalence and associated risk factors for HCC and other comorbidities in perinatally infected youth as they age into adulthood.

Acknowledgments

R.A.A. was supported by National Institutes of Health (NIH) grant 1R01DK080736.

Author Disclosure Statement

No competing financial interests exist.

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