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Case Series

Spontaneous Hepatitis B Seroclearance upon Development of Hepatocellular Carcinoma

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Abstract
The spontaneous seroclearance of hepatitis B upon development of a hepatocellular carcinoma (HCC) is extremely rare. To date, there has been one published case series reporting hepatitis B seroconversion following HCC resection. We describe two novel cases of spontaneous hepatitis B seroclearance following the development of HCC, prior to resection. Following resection, specimens were HBsAg- and HBcAg-negative in both tumor and peritumor tissues. Although the precise mechanism of this is poorly understood, nonuniform integration of hepatitis B virus DNA within the liver could lead to selective tumorigenesis of HBsAg-producing cells, explaining the observed clearance of serum HBsAg with the development of HCC.

Introduction

Despite the development of an effective vaccination program, improved antenatal screening and perinatal care, hepatitis B remains a significant cause of liver-related morbidity and mortality worldwide. There are an estimated 240 million chronic hepatitis B surface antigen-positive carriers globally [1]. Of those chronic carriers, approximately 25–40% will

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go on to develop severe complications including liver cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC) [2, 3].

Hepatitis B is a hepatotropic DNA virus from the Hepadnaviridae family of viruses. Upon infection, the hepatitis B viral DNA is incorporated into the nucleus of the hepatocyte and is converted to covalently closed circular DNA which serves as a template for the translation of all viral proteins [1].

During the acute phase of infection, stimulation of the innate and adaptive T cell immune responses leads to hepatocytolysis, release of antiviral cytokines, and the production of neutralizing antibodies from stimulated B lymphocytes. This prevents the spread of the virus and destroys infected cells. When the acute infection becomes chronic, a progressive impairment of specific T lymphocyte function is observed [1].

The natural course of chronic hepatitis B virus (HBV) infection is described by four distinct phases. The initial phase is the immune tolerant phase, consisting of high hepatitis B viral DNA levels, e antigen positivity, and normal liver enzymes. This is followed by the immune clearance phase, with reductions in hepatitis B viral DNA levels, e antigen seroconversion in conjunction with hepatic necroinflammation, and elevations of aminotransferase levels. Following these phases, patients can develop hepatitis B e antigen-negative chronic infection characterized by low viral DNA levels and persistently normal liver enzymes. In these patients, the rate of spontaneous seroclearance is estimated at 1–3% per year [3]. Alternatively, patients can develop hepatitis B e antigen-negative, chronic hepatitis, characterized by the lack of e antigen, moderate viral DNA levels, ongoing hepatic necroinflammation, and fluctuating liver enzymes. This phase is associated with low levels of spontaneous clearance. Low HBV DNA and surface antigen levels are associated with higher rates of spontaneous viral clearance [1–3].

The development of HCC is the primary concern in patients with chronic infection. HCC rates can vary from 8 to 20% in untreated patients with chronic hepatitis [2]. The risk is increased in individuals of African origin, male gender, with metabolic risk factors or those who are co-infected with other hepatotropic viruses [2]. HCC risk is reduced but not eliminated in individuals who undergo viral clearance and it is recommended that individuals with cirrhosis continue with surveillance [2, 3].

Spontaneous seroclearance of hepatitis B upon development of a HCC is extremely rare. To date, there has only been one published case series reporting hepatitis B seroconversion within months following HCC resection [4]. We describe two cases of spontaneous hepatitis B seroclearance in hepatitis B e antigen-negative patients with chronic hepatitis, upon development of HCC.

Case Reports

A 29-year-old Congolese woman complained of a 1-month history of progressive, constant, nonradiating right upper quadrant pain. Her appetite and weight had remained stable. She had been attending the clinic for 3 years, was hepatitis B e antigen negative with low HBV DNA levels (<2,000 IU/mL) and had persistently normal liver enzymes. Six months prior to her presentation, virology data reported negative e antigen status with a low viral load (69 IU/mL). She had no other relevant medical history and was a nonsmoker with no history of alcohol intake. Clinical examination was normal with no stigmata of chronic liver disease. Laboratory investigations included: WBC count 2.1 × 10^9/μL, Hb 12.9 g/dL, platelet count 150 × 10^9/L, ALT 25 IU/L, AST 17 IU/L, bilirubin 0.58 mg/dL, and albumin 45 g/L.

Alpha-fetoprotein level was 267.8 ng/mL (normal range <7 ng/mL) and urinary β-HCG was negative. At presentation, her hepatitis B viral load went undetected and a serological test for hepatitis B surface antigen was negative. She had had no interval exposure to antiviral therapy.

Triphasic CT revealed a large 6.8 × 7.8 × 5.8 cm mass in segment II and IV A of the liver consistent with HCC, BCLC stage B.

She was referred to a specialist hepatobiliary center and proceeded to an open left hemi-hepatectomy. Examination of the resection specimen demonstrated a noncirrhotic liver, Ishak stage 4, with evidence of bridging fibrosis. The tumor was well-encapsulated and demonstrated no extracapsular or portal vein invasion. Tissue HBsAg and HBcAg were negative in both the tumor and the peritumor liver resection specimen (Fig. 1).

The patient made a full recovery and 2 years following the procedure, there is no evidence of HCC recurrence and hepatitis B surface antigen remains negative. Follow-up testing for hepatitis B surface antibody and hepatitis B DNA have been persistently negative over 3 years of follow-up.

A 54-year-old Caucasian man with a history of chronic hepatitis B presented for a routine examination in a clinic. He was asymptomatic and his clinical examination was normal, with no stigmata of chronic liver disease. The patient had a history of hepatitis B e antigen-negative chronic hepatitis B, with moderate viral load and fluctuating ALT levels. He had previously been on Adefovir following an ALT flare, but self-discontinued the medication 4 years prior to presentation despite the risks. He was a smoker with occasional alcohol intake. On examination of his laboratory investigations, the HBV viral load had remained low at 139 IU/mL. A progressive rise in his α-fetoprotein level was observed over a 1-year period from 32.7 to 250 ng/mL (normal range <7 ng/mL). This mirrored a decline in his HBV DNA from 10 IU/mL but became undetected with a negative hepatitis B surface antigen. Hepatitis B surface antibody levels were 290 IU/mL. Other laboratory investigations included: WBC 10.1 × 10^9/μL, Hb 15.5 g/dL, platelet count 134 × 10^9/L, ALT 31 IU/L, AST 26 IU/L, bilirubin 0.47 mg/dL, and albumin 42 g/L.

An MRI of the liver was performed showing a 2-cm lesion in segment 8 of the liver, which demonstrated restricted diffusion with washout and a capsule, consistent with HCC, BCLC stage A.

He was referred to a specialist hepatobiliary center and proceeded to a right hemihepatectomy. Examination of the resection specimen demonstrated evidence of bridging fibrosis and nodule formation, the tumor was well encapsulated, and there was no extracapsular or portal vein invasion. Tissue HBsAg and HBcAg were negative in both the tumor and nontumoral portions (Fig. 2).

He had an uncomplicated postoperative course and had been followed up at the clinic after the resection.

Discussion

Spontaneous viral clearance of hepatitis B occurs rarely amongst patients with chronic e antigen-negative hepatitis with rates of 1–3% [1–3, 5]. Factors associated with increased clearance rates include low viral DNA, surface antigen levels, and increased duration of viral infection [2, 3]. The development of HCC following viral clearance has been well described in patients with cirrhosis [3, 5]. However, to date, there has been one published case report

describing spontaneous seroclearance in patients with HCC following tumor resection. There have been no case reports of viral clearance occurring upon development of HCC [4].

We report 2 rare cases of HBsAg seroclearance following development of HCC prior to resection in patients with chronic e antigen-negative hepatitis. The precise mechanism of this is not understood. HBV DNA integration in hepatocytes is believed to be one of the key mechanisms promoting carcinogenesis in the liver. Prior studies have shown that hepatitis B surface and core antigen are distributed in a nonuniform fashion in the liver of patients with chronic active hepatitis B [5, 6]. In vitro studies have shown the possibility of cell to cell transmission of HBV; however, this does appear to occur primarily in the early phases of acute infection [7, 8]. The nonuniform integration of viral DNA within the liver may have led to the development of HCC specifically in HBV-infected hepatocytes. The selective tumorigenesis of these specific HBsAg-producing cells may explain the observed clearance of serum HBsAg upon development of HCC [6, 9]. Both of the patients discussed had risk factors for the development of cancer (ethnicity, gender) and low HBV DNA levels prior to HCC development. Vigilance is required in assessing the severity of liver fibrosis and HCC screening in patients who demonstrate a decline in HBV viral DNA or spontaneous seroclearance, although further large-scale studies are required.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patients for publication of this case report.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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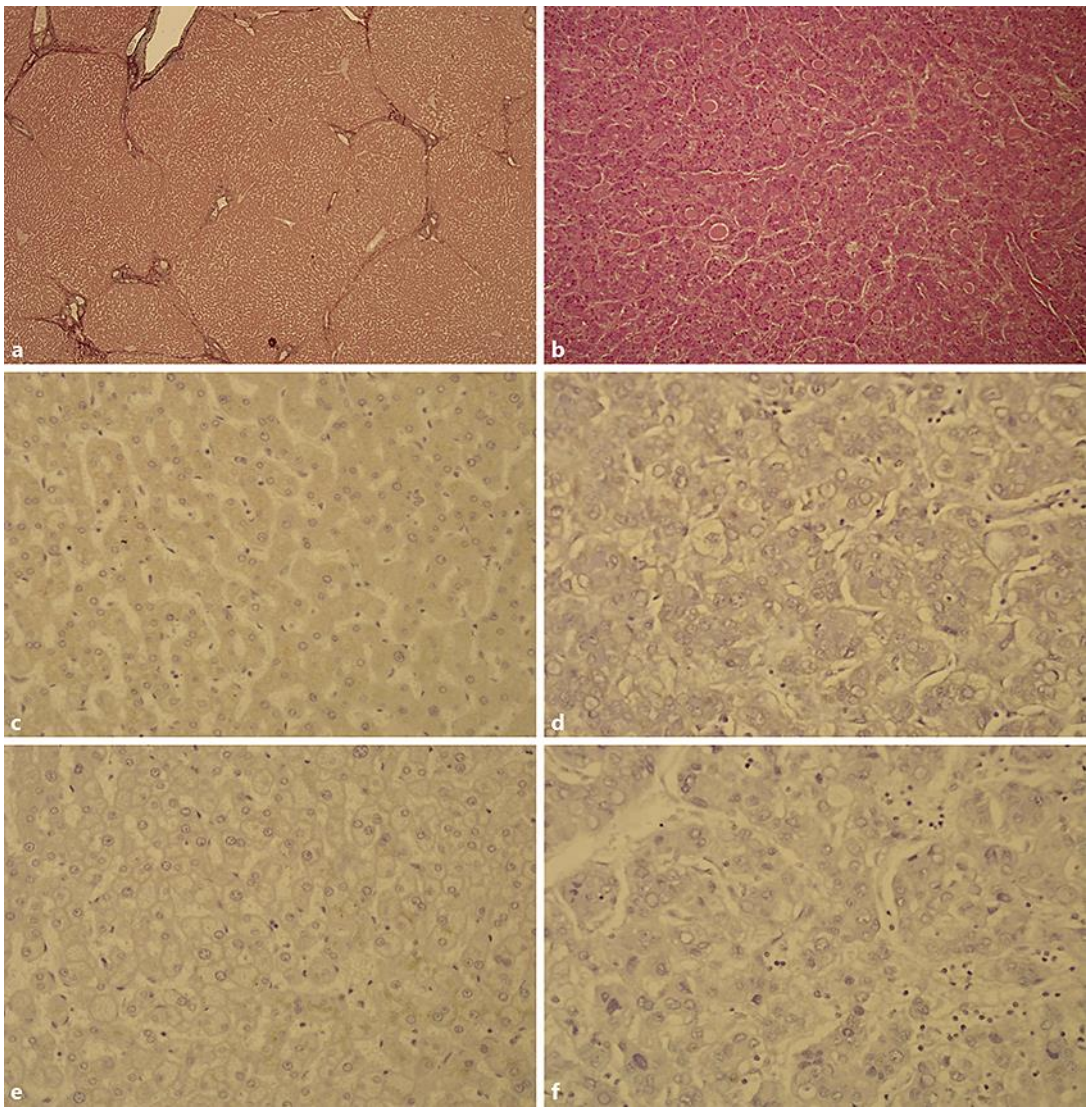

Fig. 1. **a** Background liver tissue showing bridging fibrosis (Shikata ×4). **b** Grade 2 pseudoglandular HCC (H&E ×10). **c** Negative hepatitis B core antigen immunohistochemistry in resected liver tissue (×40). **d** Negative hepatitis B core antigen immunohistochemistry in HCC (×40). **e** Negative hepatitis B surface antigen immunohistochemistry in resected liver tissue (×40). **f** Negative hepatitis B surface antigen immunohistochemistry in HCC (×40). HCC, hepatocellular carcinoma.

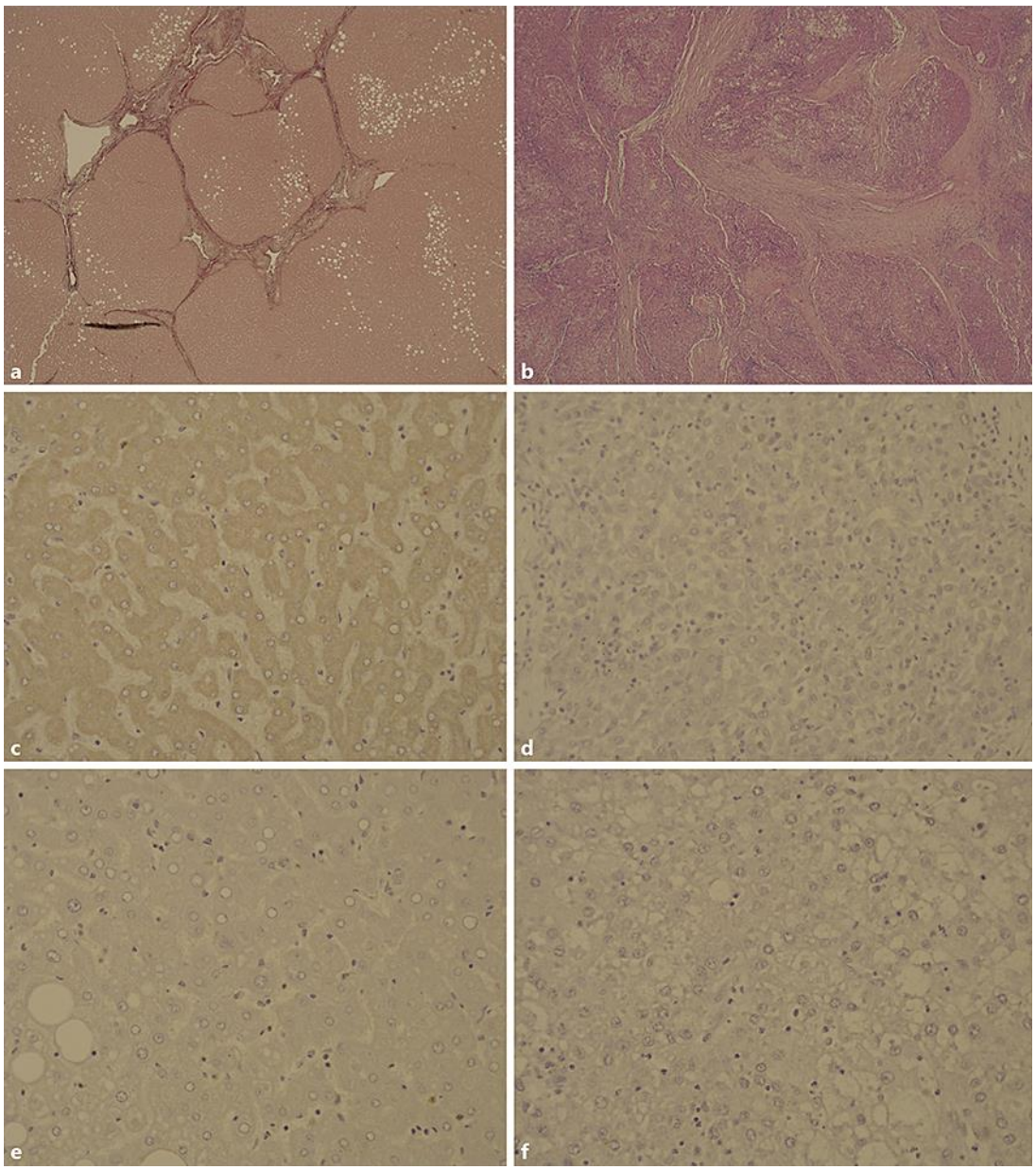

Fig. 2. **a** Nonneoplastic liver tissue with bridging fibrosis and nodule formation (Shikata ×4). **b** Trabecular and infiltrative, grade 2–3 HCC (H&E ×10). **c** Negative hepatitis B core antigen immunohistochemistry in resected liver tissue (×40). **d** Negative hepatitis B core antigen immunohistochemistry in HCC (×40). **e** Negative hepatitis B surface antigen immunohistochemistry in resected liver tissue (×40). **f** Negative hepatitis B surface antigen immunohistochemistry in HCC (×40). HCC, hepatocellular carcinoma.