Hepatocellular Carcinoma and Crohn’s Disease: A Case Report and Review

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Abstract

Hepatocellular carcinoma (HCC) is usually known to develop in patients with underlying high-risk liver diseases such as viral hepatitis, cirrhosis and alcohol abuse, whereas reports dealing with HCC in Crohn’s disease (CD) are limited. We present a case of HCC, which developed sequentially within a short period in a 52-year-old Japanese man with a 36-year history of CD without risky conditions for HCC. He also had not taken immunosuppressants such as azathioprine. Although the definitive etiological factors contributing to hepatocarcinogenesis in the present case could not be elucidated, further close surveillance is required.

Key words: hepatocellular carcinoma (HCC), Crohn’s disease (CD)

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Introduction

Hepatocellular carcinoma (HCC) is one of most prevalent primary cancers of the liver worldwide, and is known to arise almost exclusively under certain established high-risk situations. A number of major risk factors for the development of HCC have been recognized, including hepatitis B and C viral infection, chronic alcoholic abuse, liver cirrhosis from almost any etiology and rare environmental factors, such as repeated exposure to aflatoxin (1, 2). The incidence of HCC without the above circumstances is uncommon; however, HCC can occasionally develop in the healthy liver during normal aging (1). In the present patient, HCC occurred sequentially over a short period in the liver without any known risk factors for HCC, except for long-standing Crohn’s disease (CD).

CD is a chronic inflammatory disease that can affect any region of the gastrointestinal tract and is also considered a systemic disorder that often involves other organs (3). In addition, the association between CD and various cancers, especially small intestinal and colorectal carcinoma, has been demonstrated (4, 5), and reports dealing with CD and HCC have also been documented (6-10). In this clinical setting, the prescription of prolonged azathioprine (AZA) or AZA-based immunosuppressive agents was proposed to be a risk factor for the development of HCC; however, studies especially aimed at elucidating the risk of neoplasms in patients treated with AZA for inflammatory bowel disease concluded that AZA does not substantially increase the risk of cancer (11, 12). Therefore, whether AZA predisposes CD patients to HCC is still controversial, and the mechanisms of the occurrence of HCC in CD patients remain unclear.

We describe herein a rare case of HCC developing in a patient with a long 36-year history of CD without known high-risk liver diseases for HCC or a history of immunosuppressants, and review previous reports dealing with HCC concomitant in patients with CD.

Case Report

In March 2007, a 52-year-old Japanese man with a 36-year history of small bowel and colonic CD was admitted to the Social Insurance Central General Hospital for examination of a space-occupying lesion in the liver. His medical history had been significantly complicated and sometimes required surgical procedures and hospitalization since the diagnosis of CD, which was first confirmed pathologically as
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Figure 1. Abdominal enhanced CT imaging with contrast medium in March 2007. Hepatic nodules located in segment VI and VII were visualized, showing early arterial enhancement and a homogeneous defect in the delayed portal phase suggesting HCC (Fig. 1a, 1b). Splenomegaly, a dull edge of the liver and gallstones were seen; however, hepatic parenchyma other than nodular lesions appeared almost normal.

a result of subtotal colectomy at another hospital in 1971 at the age of sixteen. The patient underwent incision and drainage for worsened perianal abscess in 1975. Since 1978, several fistulous communications, including cutaneo-intestinal, vesico-intestinal and ileo-rectal fistula, had developed sequentially and had been treated symptomatically. The patient was referred to the hospital for further examination and treatment in 1987 and has attended the hospital regularly since then. In 1990, colostomy had been performed because of intractable recurrent fistulous lesions. In May 2004, subtotal ileectomy was performed because of re-worsening of the cutaneo-intestinal fistulous abscess. In addition to these surgical treatments, his medications included 5-aminosalicylic acid (5-ASA) 3 g/day, metronidazole (MNZ) 1 g/day and enteral alimentation; however, he had never taken immunosuppressive agents, such as AZA, 6-mercaptopurine and prednisolone. Over the previous 3 years, he had been in a relatively good and uneventful condition until February 2007, when he presented with bronchitis. Chest computed tomography (CT) incidentally revealed a low-density nodular lesion in the right hepatic lobe measuring 24 mm in diameter.

On admission in March 2007, he was 177.2 cm tall and weighed 60.8 kg, blood pressure was 116/72 mmHg and temperature was 36.6°C. There was no history of alcohol abuse. Physical examination revealed no abnormal findings except for colostomy and multiple well-healed scars from previous operations over his abdomen. Laboratory findings on admission were as follows: white blood cell (WBC) count, 7,760/mL (normal value, 4,000-9,000); red blood cell (RBC) count, 408×10^4/mL (normal value, 410-530×10^4); hemoglobin (Hb), 13.5 g/dL (normal value, 14-18); platelet count (Plate), 10,0×10^4/mL (normal value, 12-36×10^4); total serum protein (TP), 7.7 g/dL (normal value, 6.5-8.0); serum albumin (Alb) 3.6 g/dL (normal value, 4.1-5.1); aspartate aminotransferase (AST), 25 IU/L (normal value, 10-33); alanine aminotransferase (ALT), 16 IU/L (normal value, 4-30); alkaline phosphatase (ALP), 243 IU/L (normal value, 167-345); γ-glutamyl transpeptidase (γ-GTP), 132 IU/L (normal value, 10-75); serum total bilirubin (TB), 0.8 mg/dL (direct 0.2 mg/dL); amylase 120 IU/L (normal value, 30-120); C-reactive protein (CRP), 0.1 mg/dL (normal value, 0.0-0.4); fasting blood glucose (FBG), 105 mg/dL (normal value, 70-107). In his previous clinical course before admission, gallstones had been noted and the levels of liver enzymes, including AST, ALT, ALP and γ-GTP, were not always normal but were within twice the normal upper limits, even though they fluctuated. Alpha-fetoprotein levels were within normal limits; however, the level of protein induced by vitamin K absence II (PIVKA II) was revealed to be significantly elevated to 16,300 mAU/mL (normal value, 0-40). Hepatitis B and C serology, including anti-hepatitis B core antibody (HBeAb) was negative, as was antinuclear antibody and anti-mitochondrial antibody. He was not obese and did not have impaired glucose tolerance. Abdominal CT with contrast material demonstrated hepatic nodules located in segment VI and VII showing early arterial enhancement and a homogeneous defect in the delayed portal phase (Fig. 1a, 1b). The remaining hepatic parenchyma appeared otherwise almost normal, although a dull edge of the liver and splenomegaly were demonstrated, suggesting the presence of some chronic change (Fig. 1a). Magnetic resonance cholangiopancreatography (MRCP) showed no abnormalities in his biliary trees.

The absence of known underlying risk factors for the development of HCC, including hepatitis B and C viral infection, cirrhosis and alcohol abuse, led us to carry out a liver biopsy in order to obtain histopathological confirmation of both tumor and non-tumor regions in April 2007. Histopathology of the tumor tissues taken by fine needle aspiration biopsy from nodule in segment VII disclosed well-differentiated HCC with a high N/C ratio showing trabecular architecture adjacent to normal hepatocytes (Fig. 2a). Microscopic findings of the non-tumor region neighboring but remote from the tumor obtained randomly by core biopsy revealed almost totally well-preserved hepatic parenchyma;
Figure 2. Histopathological examination of tissues obtained from both tumors and non-tumor regions was performed in April 2007. Histopathology of the tissues taken from the tumor in segment VII by fine needle aspiration biopsy disclosed well-differentiated HCC with a high N/C ratio showing trabecular structures adjacent to normal hepatocytes (Hematoxylin and Eosin staining) (Fig. 2a). On the other hand, microscopic findings of the non-tumor region neighboring but remote from the tumor obtained randomly by core biopsy revealed totally well-preserved hepatic parenchyma; however, mononuclear cell infiltration and fibrosis in the portal area suggesting some chronic liver inflammation were observed (Masson trichrome staining) (Fig. 2b).

Figure 3. Abdominal angiography revealed additional hypervascular tumor stains other than the originally detected nodules; therefore, transcatheter arterial chemoembolization (TACE) was carried out according to the guidelines for the treatment of HCC in Japan. The architecture of intrahepatic arteries was distorted by hepatic subcapsular hematoma. However, mild mononuclear cell infiltration and fibrosis in the portal area were seen, suggesting some chronic liver inflammation (Fig. 2b). Subsequent to liver biopsy, the patient was complicated with hepatic subcapsular hematoma presumably caused by an aspiration biopsy; therefore, hepatic angiography was performed for the evaluation of subcapsular hematoma as well as HCC progression. Upon hepatic angiography, no extravasation of blood suggestive of active bleeding was observed; however, additional hypervascular tumor stains other than the original nodules were visualized, and transcatheter arterial chemoembolization (TACE) was selected for treatment according to the guidelines for the treatment of HCC in Japan (Fig. 3). The PIVKAII level post-TACE decreased to 1,260 mAU/mL but was not normalized, and was consistently high, around 1,000-2,000 mAU/mL thereafter, suggesting residual subclinical viable HCC or buds of intrahepatic metastasis. As suspected, in December 2007, an ectopic HCC nodule in segment VIII, 14 mm in diameter, emerged, and another HCC located in segment V, over 10 mm in diameter, was detected on follow-up imaging in June 2008. Additional TACE and radio-frequency ablation therapy were performed. No recurrence was seen on CT imaging in December 2008; however, as the levels of PIVKAII currently remain high, 1,980 mAU/mL, further careful surveillance for HCC is mandatory.

Discussion

This case report presents important clinical issues when dealing with patients with long-standing CD; that is, HCC can occur in patients with long disease history of CD, even without underlying high-risk liver diseases for HCC or a history of using immunosuppressant agents. CD is a chronic inflammatory disease that can affect any region of the gastrointestinal tract and is also considered a systemic disorder that often involves other organs (3). In addition, the close link between CD and malignancy, especially small intestinal and colorectal carcinoma, has been demonstrated (4, 5). When HCC becomes a problem during the course of CD, it is in the clinical setting that CD is found to be complicated by primary sclerosing cholangitis (PSC) (13). PSC is a chronic cholestatic liver condition of unknown etiology resulting in biliary cirrhosis, often requiring liver transplantation, and is known to occur frequently in association with inflammatory bowel diseases (IBD). Hitherto, two reports on HCC arising in CD patients in the presence of PSC have been described (14, 15). Upon MRCP imaging, however, the present patient was not complicated...
Table 1. Clinical Background of Cases of HCC Arising in CD

| Case No. | Onset of HCC (y.o.) | Gender (M/F) | CD duration (years) | Affected intestine | Medications for CD | Surgery for CD | CBsAg | HCV-Ab | AST (IU/L | Nodules | Largest size (cm) | AFP (ng/mL) | HCC pathology | Non-HCC pathology | Liver cirrhosis | Treatment | Course of HCC | Recurrence | Present case |
|----------|---------------------|--------------|---------------------|-------------------|-------------------|-----------------|--------|--------|--------|---------|----------------|-------------|-------------|----------------|----------------|------------|------------|-------------|------------|-------------|
| 1        | 43                  | F            | 14                  | S                 | Aza              | (-)            | (-)    | N.D.  | 16     | 1 Multiple | 7.5 × 6     | N.D.        | N.D.         | Normal         | (-)         | (-)        | Died        | N.D.       | Died        |
| 2        | 22                  | F            | 13                  | S+C               | Aza              | (-)            | (-)    | (-)   | N.D.  | 1                | 55,000      | N.D.        | N.D.         | Normal         | (-)         | (-)        | Died        | N.D.       | Died        |
| 3        | 33                  | M            | 20                  | S+C               | Aza              | (-)            | (-)    | (-)   | N.D.  | 1                | 2.3 × 2.7   | N.D.        | Trabecular   | Trabecular     | (-)         | (-)        | Died        | N.D.       | Died        |
| 4        | 28                  | M            | 14                  | S+C               | Aza              | (-)            | (-)    | (-)   | N.D.  | 1                | 26.9        | 15          | Trabecular   | Trabecular     | (-)         | (-)        | Died        | N.D.       | Died        |
| 5        | 37                  | M            | 18                  | S+C               | Aza              | (+)            | (-)    | (-)   | N.D.  | 1                | 16,300      | N.D.        | Trabecular   | Trabecular     | (-)         | (-)        | Died        | N.D.       | Died        |
| Present  | 52                  |              | 36                  |                   | Aza              | (+)            | (+)    | (+)   | N.D.  | 4 Multiple |             |             |             |               |             |            |             |            |             |

HCC, hepatocellular carcinoma; M, male; F, female; CD, Crohn's disease; S, small bowel; C, colon; N.D., not described; Aza, azathioprine; PsL, prednisolone; 5-asa, 5-aminosalicylic acid; IbsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C antibody; MNZ, metronidazole; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; PIVKAII, protein induced by vitamin K absence II; FbG, focal hepatic glycogenosis; CLD, chronic liver damage; TACE, transarterial chemoembolization

with PSC. Five other reports have dealt with CD patients who developed HCC without any established risk factors for HCC (6-10). The clinical backgrounds of these five cases, in addition to our case, are listed in Table 1. The average age of these previously reported five cases was 32.6 years old, which seems significantly younger than the age at which HCC most commonly occurs (2). The man: woman ratio was even. The average time to HCC development from the onset of CD was 15.8 years. The affected region of the intestine or history of surgery did not show a definite tendency. Although information on hepatitis C in an earlier case was not available, all reported cases were negative for viral hepatitis B and C serology and were non-cirrhotic; however, all previous cases had a common clinical background, that is, they were all treated with AZA or AZA-based combination therapy. AZA is a drug widely prescribed for organ transplantation to reduce rejection and autoimmune diseases or IBD as a steroid-sparing agent. An increased risk of a variety of malignancies subsequent to AZA has been demonstrated, especially non-Hodgkin’s lymphoma and cutaneous squamous carcinoma (16, 17); in addition, HCC cases in renal transplant patients without apparent risk factors other than long-standing AZA therapy have been published (18). The mechanisms by which patients treated with AZA are predisposed to malignancy are thought to be direct toxicity and mutagenic effects, enhanced susceptibility to oncogenic viruses and decreased immunological surveillance for neoplasms (19). As for HCC presumably related to AZA, some reports have described that focal hepatic glycogenosis (FHG) played a preneoplastic role in the development of HCC (7, 9), whereas there are other reports of IBD patients treated with AZA that failed to detect an increased risk of malignancy (11, 12). Therefore, whether AZA predisposes CD patients to malignancy, including HCC, is still controversial.

The present case had no established risk factors for the development of HCC and had not been given immunosuppressive drugs, including AZA. Why did several HCC nodules occur sequentially over a short period in this case? Approximately up to 90% of all detected HCC cases in Japan occur with hepatitis B and C viral infection (20, 21), however, half of the remaining HCC cases are of unknown origin (21), and HCC can arise even in normal liver (1, 22). In addition, regardless of risk, the rates of HCC increase progressively with aging (2). The present patient was far older than the other five HCC cases listed in Table 1; therefore, it is possible that HCC developed coincidentally without any association with CD in the present case. Another probability is that long-standing CD could be involved in the occurrence of HCC. Even without known hepatic diseases, the liver in long-term CD patients is often susceptible to non-specific inflammation of other causes, such as drug-induced adverse reactions, cholecystitis due to gallstones that frequently complicated in CD (23), and hepatic steatosis or nonalcoholic steatohepatitis from malnutrition (24) or small bowel excisions (25) etc. Etiologically, repeated liver damage from any causes resulting in hepatic fibrotic progression can be risk factor for HCC by leading to chromosomal damage. Indeed, the patient presented here had had several clinical manifestations with fluctuation of liver enzymes over a long CD duration of 36 years, including a history of prolonged medication, gallstones and malnutrition from short bowel syndrome. Although extensive liver fibrosis or cirrhosis was not seen, the histopathology showed chronic liver inflammation, and the morphological appearance on CT imaging also suggested the presence of chronic liver damage or at least portal hypertension. Therefore, in the present case, HCC could potentially develop against the background
of chronic liver conditions influenced by long-term CD history. Resected specimens are required to fully analyze the underlying liver disease.

The association between CD and hepatocarcinogenetic potential is unknown; however, considered in conjunction with the above five reports regarding CD and HCC, in addition to the present case, a potential correlation between long-standing CD and the development of HCC may exist. Although the condition is relatively rare, further cumulative clinical investigation is necessary to elucidate the link between CD and HCC.

References