

Large Intrahepatic Cholangiocarcinoma with Tumor Infiltrative Lymphocytes and Autoimmune Hepatitis-Like Features

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Key Words

Intrahepatic cholangiocarcinoma · Autoimmune hepatitis · Tumor infiltrative lymphocyte

Abstract

The development of a primary hepatic tumor associated with autoimmune hepatitis (AIH) has been rarely reported. This report describes a rare case of intrahepatic cholangiocarcinoma (ICC) that accompanied tumor infiltrative lymphocytes (TIL) and AIH-like features. Moreover, multiple early gastric cancers were recognized in synchrony. An 81-year-old male was admitted due to liver dysfunction. His laboratory data on admission showed an elevation of immunoglobulin G and a positive titer of antinuclear antibody. Biological tests for HBV and HCV were negative. Computed tomography showed a well-enhanced hepatic tumor and gastrointestinal fiberscopy revealed two early gastric cancers with mucosal invasion. Biopsies were obtained from the background liver and the hepatic tumor. Histologically, the tumor revealed adenocarcinoma and the liver showed piecemeal necrosis and interface hepatitis with lymphoplasmacytic infiltration. The patient underwent hepatectomy and distal gastrectomy. Finally, he was diagnosed to have a mass forming type ICC and early gastric cancers. Moreover, prominent TIL in the ICC was revealed. An analysis of the infiltrating lymphocytes by immunohistochemical staining suggested that there was a difference in the local immune response between the tumor and the background liver. Review of the literature showed that there are only three reports of ICC associated with AIH, if including the current case.

Introduction

Recently, as the survival of autoimmune hepatitis (AIH) has improved due to steroid therapy, the number of hepatocellular carcinomas (HCC) observed in association with AIH have increased [1, 2]. AIH accompanied by malignant tumors such as HCC, intrahepatic cholangiocarcinoma (ICC), colon cancer, gastric cancer and cervical cancer of the uterus have been reported previously [1–6]. However there are only two reports of ICC associated with AIH [3, 4]. Moreover, histological features such as tumor infiltrative lymphocytes (TIL) in ICC are rarely shown. We describe a rare case of ICC with TIL and AIH-like features.

Case Report

An 81-year-old male was admitted due to liver dysfunction. He had no significant symptoms and there was no history of alcohol abuse or medication. Laboratory data on admission showed: albumin, 3.1 g/dl; total bilirubin, 1.3 mg/dl; aspartate aminotransferase (AST), 522 IU/l; alanine aminotransferase (ALT), 567 IU/l; alkaline phosphatase, 567 IU/l; plasma indocyanine green K, 0.1035; immunoglobulin G, 1,973 mg/dl; immunoglobulin M, 32 mg/dl. The anti-nuclear antibody (ANA) titer was 1:40 positive. Anti-mitochondria (AMA), anti-kidney-liver-microsome, anti-smooth muscle and peripheral anti-neutrophil cytoplasmic antibodies (pANCA) were all negative. DR1 and DR4 were positive among the human leukocyte-associated antigens (HLA). Hepatitis B and C virus (HBV and HCV) markers were negative, including HBV DNA by polymerase chain reaction (PCR) and HCV RNA by real-time PCR. The serum α -fetoprotein and protein-induced vitamin K absence II levels were within the normal limit at 4 ng/ml and 17 mAU/ml, respectively, but the CA19-9 level was elevated at 99 U/ml.

Dynamic computed tomography (CT) showed a well-enhanced, 60 mm mass in the early phase (fig. 1) and delayed enhancement in the late phase in segment 3 of the liver. Celiac angiography demonstrated early staining at the same site. Biopsies were obtained from the background liver and the hepatic tumor. Histologically, the tumor revealed adenocarcinoma and the liver showed piecemeal necrosis and interface hepatitis with lymphoplasmacytic infiltration (fig. 2). The patient's score according to the International Autoimmune Hepatitis Group criteria [7] was: ALP:AST (or ALT) ratio was <1.5 (+2), IgG above normal was 1.0–1.5 (+1), ANA titer was 1:40 (+1), no hepatitis viral markers (+3), no drug history (+1), no alcohol intake (+2), liver histology showed interface hepatitis (+3) and predominantly lymphoplasmacytic infiltration (+1). Therefore, his pretreatment total score was 14 points corresponding to a probable AIH. Gastrointestinal fiberoscopy was performed for further examination and two cancerous lesions with both IIC type and mucosal invasion were recognized at the angle and antrum of the stomach. Biopsy specimens obtained from these two lesions both revealed tubular adenocarcinomas. No examination of *Helicobacter pylori* infection was performed. The patient was diagnosed to have double primary cancer of a mass forming type ICC with AIH-like features and early gastric cancers.

In July 2007, a hepatectomy and distal gastrectomy with lymphadenectomy were performed. The hepatic specimen contained a well-demarcated and white to yellow tumor (62 × 30 mm in size). The histological features revealed abundant fibrosis and apparent tubular structures of cancer cells that were equivalent to moderately differentiated tubular adenocarcinoma with prominent TIL and many lymphatic follicles in the periphery of the tumor (fig. 3), but without invasion of the vessel, lymphatic and intrahepatic metastases. The components of HCC were not included throughout the entire tumor. In the background liver, interface hepatitis with lymphoplasmacytic infiltration was recognized, but no centrilobular necrosis and rosette formation of liver tissue. Considering the histological and clinical features, the patient was diagnosed as having a probable AIH. Moreover, the grading and staging of this chronic hepatitis with moderate activity and periportal fibrous expansion was A2F1 according to the New Inuyama classification. The stomach specimen demonstrated two small IIC lesions, but the histological features revealed three lesions that were all well-differentiated tubular adenocarcinomas with mucosal invasion at the angle and antrum. Immunohistochemically, the hepatic tumor was positive for Alcian blue and periodic acid Schiff double staining, CA19-9 and cytokeratin 7 and negative for cytokeratin 20 and a specific anti-human hepatocyte antibody. On the contrary, the three stomach lesions were all negative for cytokeratin 7 and 20. The gastric cancers were all mucosal carcinoma and their staining patterns of cytokeratin 7 and 20 were different from the pattern of the hepatic tumor. As a

result, finally he was diagnosed as having double primary cancer of a mass forming type ICC and early gastric cancers. According to the analysis of the infiltrative lymphocytes in the tumor and the background liver by immunohistochemistry (IHC) of CD3, 4, 8 and 20, CD3+ T cells were more predominantly stained than CD20+ B cells at the portal area and interface hepatitis in the background liver. In the tumor CD20+ B cells were diffusely stained in lymphatic follicles and infiltrative lymphocytes and CD3+ T cells were partially stained among the infiltrative lymphocytes (fig. 4). Moreover, in the background liver, CD8+ T cells were predominantly stained at the interface hepatitis and CD4+ T cells in the portal area, but in the tumor no superiority between CD8+ and CD4+ T cells was identified.

Because of his age, only ursodeoxycholic acid was administered during the pre- and postoperative period. Twenty-eight months after the operation he had no evident recurrence. The ANA titer and IgG level were 1:40 positive and 1,860 mg/dl with normal AST and ALT level.

Discussion

AIH is a chronic form of hepatitis with hypergammaglobulinemia and positive autoantibodies and the characteristic features of its histology are piecemeal necrosis and interface hepatitis with lymphoplasmacytic infiltration. However, piecemeal necrosis and interface hepatitis are observed in viral hepatitis too, therefore the difference between viral hepatitis and AIH appears to be the existence of a predominantly lymphoplasmacytic infiltration. In this case, the specimen of the liver biopsy showed the characteristic histological features of AIH, but the clinical features showed a low ANA titer and IgG with high AST and ALT at admission. These data were not typical of AIH, but instead were considered to indicate acute-onset AIH [8, 9]. On the other hand, the characteristic histological features and IHC in acute-onset AIH include interface hepatitis and centrilobular necrosis, CD4+ T cells were predominant in the portal inflammation, CD8+ T cells at the interface hepatitis and lobular hepatitis and CD79α+ B cells at the interface hepatitis and portal inflammation [9]. In this case, no evident centrilobular necrosis was observed, but features of IHC (CD4+ T cells were predominantly stained at the portal area, CD8+ T cells at interface hepatitis and CD20+ B cells at the portal area and interface hepatitis) considerably resembled the above findings. Finally the possibility of acute-onset AIH was suggested.

AIH accompanied by malignant tumors such as HCC, ICC, colon cancer, gastric cancer and cervical cancer of uterus have been reported previously [1–6]. In particular, the number of HCCs associated with AIH extends to 100 [2]. Liver cirrhosis and repeated liver damage by the autoimmune response are considered to be risk factors of hepatocarcinogenesis in AIH [1, 2]. On the other hand, according to a search of PubMed and Ichushi Web with key words of ICC and AIH for the period of 1983 to 2008, there were only two reports of ICC associated with AIH [3, 4]. Two cases had liver cirrhosis, moreover one case had progressive bile stasis and another had gallstones and common bile duct stones. These cases had high risk factors of developing ICC and the possibility that repeated damage to the bile duct cells by chronic inflammation and bile stasis contributed to the occurrence of ICC was suggested [3, 4]. In conclusion, there were no reports that AIH contributed to carcinogenesis of the bile duct. The current case did not have risk factors such as hepatolithiasis, anomalies of the biliary tree, virus infection, alcoholic history or liver cirrhosis [10]. Histologically, proliferations of cholangiole and lymphocytic infiltration around bile ducts were partially recognized, but the degree of bile duct injury was slight. Therefore, whether chronic inflammation associated with AIH contributed to the carcinogenesis of ICC remained unclear. Moreover, it was difficult to determine whether or not the patient had overlap syndrome of AIH and PBC or PSC because of the negative AMA and pANCA findings and the lack of any pathological

features, such as chronic nonsuppurative destructive cholangitis and onion skin fibrosis. Recently carcinogenesis derived from hepatic stem cells was reported, but the histological features of this case did not match [11]. In this case, the possibility that ICC occurs at the stage of not only cirrhosis, but also chronic hepatitis with AIH-like features was suggested, but the mechanism of carcinogenesis was unclear. On the other hand, it is quite possible that the complication of gastric cancer in this case was accidental because it is quite common at that age.

So far, there have been no reports of TIL occurring in malignant tumor associated with AIH. TIL is occasionally recognized in HCC, gastric cancer, ovarian cancer etc. and it was considered to be associated with good prognosis [12–14]. In fact, this case had a large mass forming type ICC, however vessel invasion, lymphatic and intrahepatic metastases were not shown and he had no evident recurrence at twenty-eight months after hepatectomy. TIL appears to contribute to inhibit the local invasion and distant metastasis. Kasper et al. reported that liver TIL consists of intratumoral CD8+ T cells and peritumoral CD4+ T cells independent of histogenetic origin [15]. In this case, CD20+ B cells were more predominantly stained than CD3+ T cells (no superiority between CD4 and CD8 was identified) in the tumor. In contrast, in the background liver CD3+ T cells (CD8 was predominant) were more predominantly stained than CD20+ B cells. As a result, the local immune response was suggested to differ between the tumor and the background liver. Wada et al. reported that the better prognosis of HCC with TIL could therefore be attributed to the anti-tumor effect induced by the cellular immunity of CD8+ and CD4+ T cells and partly by the humoral immunity of B cells that formed lymph follicles [12]. Further accumulations of similar cases will be needed to determine whether local immune response such as TIL contributes to the prognosis of ICC.

Fig. 1. Abdominal dynamic computed tomography showed a well-enhanced 60 mm mass in the early phase at segment 3 of the liver.

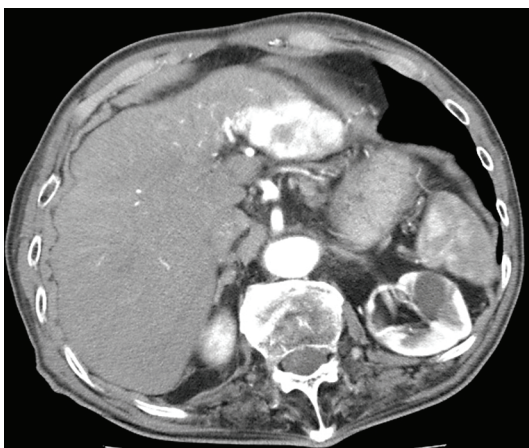


Fig. 2. Histological features of liver biopsy showed piecemeal necrosis and interface hepatitis with lymphoplasmacytic infiltration. PAS, $\times 100$.

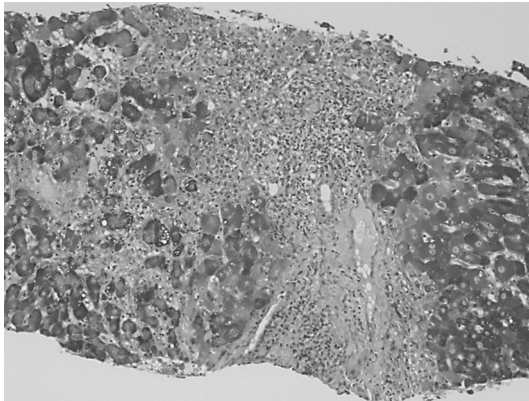


Fig. 3. Histological features revealed a moderately differentiated tubular adenocarcinoma with tumor infiltrative lymphocytes and lymphatic follicles. HE, $\times 100$.

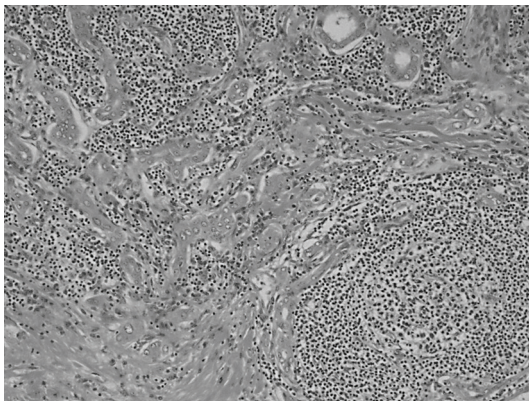
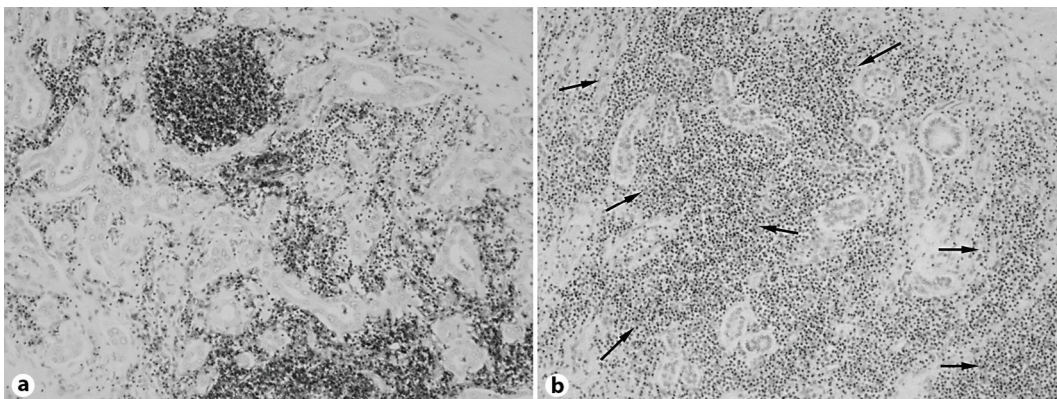


Fig. 4. In the tumor CD20+ B cells were diffusely stained at lymphatic follicles and infiltrative lymphocytes (a), but CD3+ T cells were partially stained at infiltrative lymphocytes (b, arrows). $\times 100$.



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