BRIEF COMMUNICATION

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A Case of Colonic Adenocarcinoma in a Patient with Wilson's Disease

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Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism that results in the accumulation of copper in the body and primarily in the liver, brain, and cornea. Copper is a toxic metal and might be associated with cancer induction. Most malignancies associated with WD are hepatocellular carcinoma and cholangiocarcinoma. Other intra-abdominal malignancies have been only rarely reported. To our knowledge, this is the first report to suggest that patients with WD may be vulnerable to a malignant change in the colonic mucosa during long-term copper chelating therapy. We report a case of colonic adenocarcinoma in a patient with WD and review the related literature. **(Gut Liver 2013;7:500-503)**

Key Words: Hepatolenticular degeneration; Copper; Malignancy; Colon; Adenocarcinoma

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism.[1,2] WD occurs worldwide with an average prevalence of ~30 affected individuals per million.[1] In Korea, a nationwide survey conducted in 2004 revealed that the prevalence of WD was approximately 1/90,000.[3] WD is caused by mutation of the ATP7B gene encoding ATP7B protein (copper-transporting P-type ATPase), the central regulator of hepatic copper metabolism.[4] Clinically, WD is accompanied by hepatic damage and neurological disturbance of variable degree.[5] Hepatic damage becomes manifest in approximately 40% of affected patients. These patients either present acutely with liver failure, hemolytic anemia, or both or more chronically with liver conditions such as chronic hepatitis, portal hypertension, or cirrhosis. In other patients, liver disease remains subclinical, while copper levels increase in other parts of the body as result of ongoing copper accumulation. These patients generally present with neuropsychiatric manifestations, including movement or dystonic disorders, dysarthria and behavioral disturbances.[5] Patients with WD may present with important extrahepatic manifestations apart from neurologic or psychiatric disease, including ocular abnormalities such as Kayser-Fleischer rings and sunflower cataracts, renal abnormalities including aminoaciduria and nephrolithiasis, skeletal abnormalities such as premature osteoporosis and arthritis, cardiomyopathy, pancreatitis, hypoparathyroidism, and infertility or repeat miscarriages.[1,2]

Copper is a toxic metal and might be expected to be associated with cancer induction, as is iron in hemochromatosis. Although over 50% of patients with WD also have chronic liver disease, the incidence of hepatocellular carcinoma (HCC) is less common than other etiologies.[6,7] In addition, most of the malignancies associated with WD are HCC or cholangiocarcinoma, with other intra-abdominal malignancies very rarely reported.[8] In this study, we report the first case of colonic adenocarcinoma in a patient treated for WD and review the related literature.

CASE REPORT

A 34-year-old male was admitted to our hospital due to abdominal pain and constipation of 1-month duration. Five years previously, the patient was diagnosed with WD. Laboratory examination results at the time of diagnosis of WD revealed the following blood chemistry: white blood cells 3,600/mm^3, hemoglobin 14.1 g/dL, platelets 97,000/mm^3, aspartate aminotransperas (AST) 37 IU/L, alanine aminotransferse (ALT) 57 IU/L, gamma-glutamyl transpeptidase 100 IU/L, alkaline phosphatase 229 IU/L, total bilirubin 1.83 mg/dL, albumin 4.1 g/dL, serum ceruloplasmin 2.3 mg/dL (normal range, 20 to 40 mg/dL), serum copper 47 μg/dL (normal range, 90 to 130 μg/dL), and 24-hour urinary copper excretion 421 μg (normal range, <40 μg). Other

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serologic markers were all negative. Slit-lamp examination revealed a band of golden-brownish pigment in the cornea, i.e., a Kayser-Fleischer ring (Fig. 1). Abdominal ultrasonographic findings were compatible with liver cirrhosis. The patient was diagnosed with WD and treated with D-penicillamine (1.5 g/day), adjusted according to the amount of 24-hour urinary copper excretion.

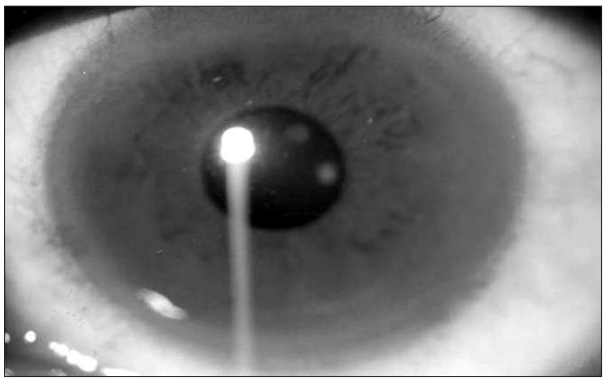

Fig. 1. Slit-lamp examination revealed a band of golden-brownish pigment in the cornea: i.e., a Kayser-Fleischer ring.

At admission, vital signs were blood pressure 110/70 mmHg, pulse 100 beats/min, respiration 20/min, body temperature 36°C, and body mass index was 23.5 kg/m^2. He was a nonsmoker and had no prior or family history of colon cancer. Laboratory examination results showed hemoglobin 11.9 g/dL, serum albumin 3.8 mg/dL, total bilirubin 1.1 mg/dL, AST 24 IU/L, ALT 18 IU/L, prothrombin time (INR) 1.1, serum ceruloplasmin 3.5 mg/dL, 24-hour urinary copper excretion 752 μg, serum carcinoembryonic antigen 13.3 ng/mL. Abdominal computer tomography scan showed localized thickening of the wall of hepatic flexure with an irregular mass-like lesion protruding into the lumen. Colonoscopic examination revealed ulceroinfiltrating mass at the hepatic flexure leading to luminal stenosis (Fig. 2A). Positron emission tomography-computed tomography scan showed increased uptake of 18-fluoro-fludeoxyglucose at the hepatic flexure of the ascending colon (Fig. 2B) but no lymph node or distant metastatic lesion. The patient underwent exploratory laparotomy with right hemicolectomy. The gross appearance

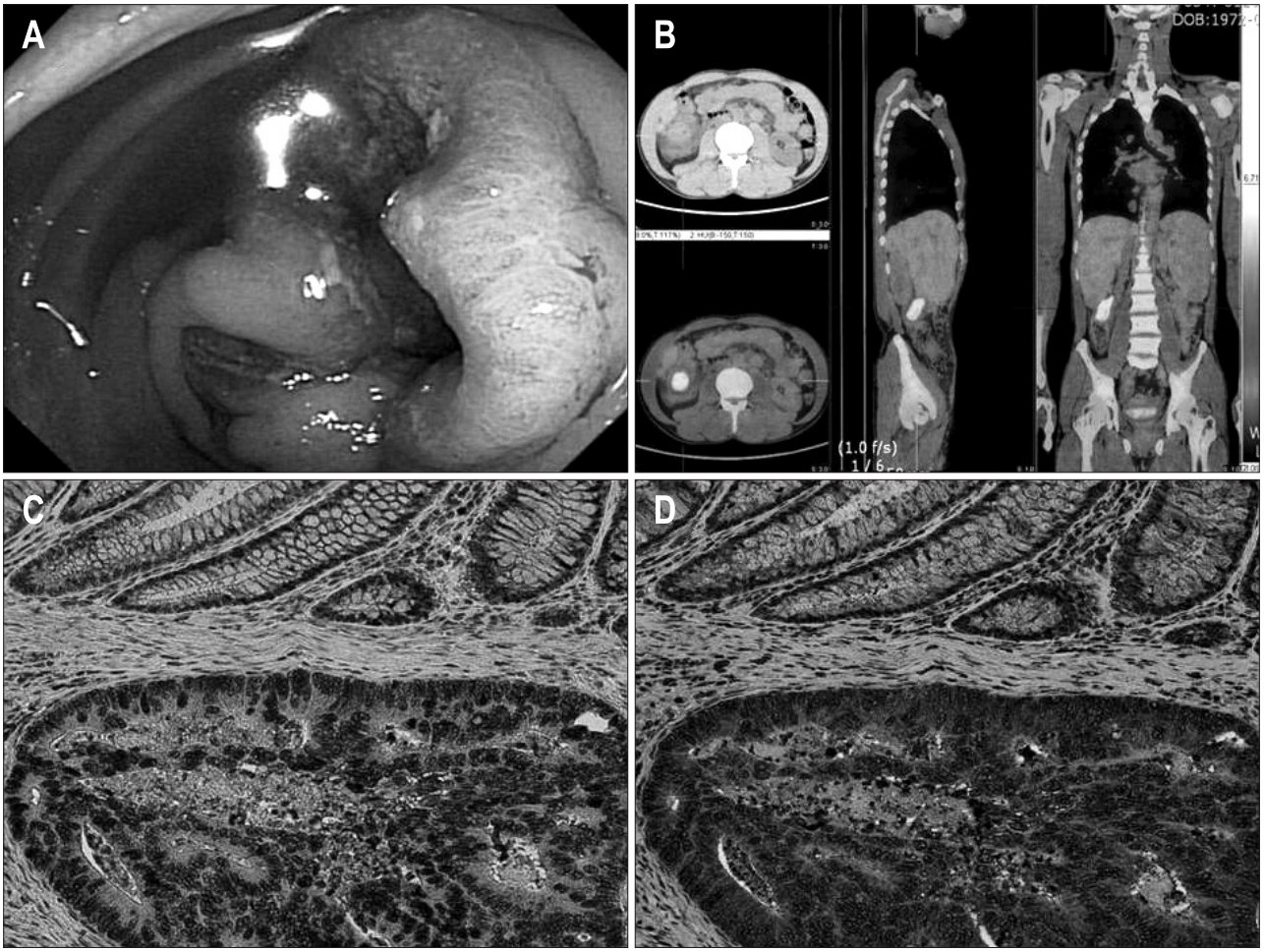

Fig. 2. (A) Colonoscopy revealed a large ulceroinfiltrative mass lesion in the hepatic flexure. (B) Positron emission tomography-computed tomography scanning indicated increased uptake of 18-fluoro-fludeoxyglucose in the intraluminal mass in the hepatic flexure. (C) Immunohistochemical staining indicated intact expression of hMSH2 and (D) loss of hMLH1 expression (×200).

of the resected specimen showed a 6.0×5.0 cm-sized, centrally ulcerative mass, and histologic analysis revealed moderately differentiated adenocarcinoma. Immunohistochemical staining showed intact hMSH2 expression but loss of hMLH1 expression (Fig. 2C and D). The final surgical staging was pT3N0M0. There were no postoperative complications, and the patient has been followed at the outpatient clinic without recurrence for 2 years.

DISCUSSION

Catalytic copper, due to its mobilization and redox activity, is believed to play a central role in the formation of reactive oxygen species, such as superoxide anion ($O_2^{\cdot-}$) and hydroxyl radicals ($^{\cdot}OH$), that rapidly bind to DNA and produce damage by breaking the DNA strands or modifying the bases and/or deoxyribose, leading to carcinogenesis.[9] Copper is also involved in tumor angiogenesis via stimulation of the proliferation and migration of endothelial cells and activation of several proangiogenic factors.[10] It has been shown that serum copper concentration increases with cancer progression and correlates with tumor incidence and burden.[11,12]

With prolonged survival periods observed in patients with WD due to improved prognosis by administration of a copper chelator, the frequency of HCC has been reported to be increased in WD patients.[13] Walshe *et al*.[8] reported that patients with WD appear to be vulnerable to the formation of aggressive malignant intra-abdominal tumors during long-term follow-up, irrespective of treatment. In that study, nine (5.7%) of 159 patients with WD had abdominal malignancies including HCCs, cholangiocarcinomas, and poorly differentiated adenocarcinomas of undetermined primary site. However, other intra-abdominal malignancies have been only rarely reported. To our knowledge, this is the first report to suggest that patients with WD may be vulnerable to malignant change in the colonic mucosa during long-term copper chelating therapy. The role played by free radicals in the pathogenesis of colorectal cancer has been strongly suggested by experimental and clinical research. The creation of free radicals through the Fenton reaction has been proposed to explain the association among high dietary iron, red meat, and colorectal cancer.[14] The relationship between copper and neoplasms has mainly been investigated in copper-deficient diets in experimental models. A recent review of the literature stated that experimental support for the relevance of oxidative damage due to the mechanisms of metal toxicity and carcinogenicity was particularly strong for copper.[15] In addition, a case control study from France revealed that high dietary iron and copper were associated with an overall increased risk of colorectal cancer.[16]

It is still unclear whether or not the colonic adenocarcinoma in our patient was purely coincidental. In the study by Walshe *et al*.,[8] they had taken 10 years as a cutoff point, since the shortest duration of follow-up before the development of cancer was 11 years. In contrast, this patient was diagnosed as WD only 5 years before the diagnosis of colonic cancer. However, the risk of developing colorectal cancer generally increases with advancing age.[17] More than 90% of cases occur in people aged 50 or older, a groups to which our patient did not belong. In addition, our patient has no other risk factors, including inflammatory bowel disease, a personal or family history of colorectal cancer, obesity, diabetes, smoking, or dietary factors. It is also needed to differentiate hereditary nonpolyposis colorectal cancer (HNPCC). The inactivation of mismatch repair genes (mainly hMSH2 and hMLH1) is involved in the development of tumors in patients with HNPCC.[18] In this patient, expression of hMSH2 was intact, whereas, expression of hMLH1 was lost. However, deficiency of these mismatch repair genes is not specific to HNPCC, as it also occurs in 15% of sporadic colorectal cancers. Besides, our patient had no other malignancy or family member with colorectal cancer.

In conclusion, patients with WD treated with copper chelating therapy do seem to be at risk of developing intra-abdominal malignancies other than HCC or cholangiocarcinoma, and this risk might be associated with colon cancer. Accordingly, as the treatment duration of patients became longer, it seems that physicians need to maintain careful monitoring for early detection of the rare development of intra-abdominal malignancy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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