



## Ulcerative Colitis Associated with Cholangiocellular Carcinoma: A Case Report and Literature Review

Lei Li<sup>1</sup>, Ying Fang<sup>1</sup>, Ruofan Sheng<sup>2</sup>, Yujen Tseng<sup>1</sup>, Xizhong Shen<sup>1</sup> and Jiyao Wang<sup>1\*</sup>

<sup>1</sup>Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

<sup>2</sup>Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

### Abstract

A 24-year-old female patient has a history of Ulcerative colitis (UC) for 14 years and was treated with mesalazine. Her UC symptoms were alleviated after administration of mesalazine, however, she was repeatedly found to have abnormal liver function. The diagnosis of Cholangiocellular Carcinoma (CCC) was made via ultrasound and magnetic resonance imaging. Clinical data of the patient was retrospectively analyzed and relevant literature was reviewed to investigate the possibility for Ulcerative Colitis (UC) to progress to Cholangiocellular Carcinoma (CCC). A review of the literature suggested that UC is commonly associated with concomitant primary sclerosing cholangitis, which progresses to CCC in 11% of cases. Clinicians should be aware that UC may progress to CCC. UC patients with recurrent abnormal liver function, especially in those with serum alkaline phosphatase elevation, should undergo relevant examinations to clarify diagnosis.

**Keywords:** Ulcerative colitis; Primary sclerosing cholangitis; Cholangiocellular carcinoma

### Introduction

Primary Sclerosing Cholangitis (PSC) is the most common hepatobiliary complication related to ulcerative colitis (UC). The majority of PSC cases ultimately progress to end-stage liver disease, and ~11% are associated with concomitant Cholangiocellular Carcinoma (CCC). This study provides a clinical analysis of a UC patient with concomitant CCC and a review of relevant literature was conducted to raise awareness regarding possible progression of UC to CCC.

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#### \*Correspondence:

Jiyao Wang, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, Shanghai 200032, China, Tel: 021-64041990-2924; E-mail: wangjiyao@zs-hospital.sh.cn

Received Date: 08 Apr 2017

Accepted Date: 04 May 2017

Published Date: 06 May 2017

#### Citation:

Li L, Fang Y, Sheng R, Tseng Y, Shen X, Wang J. Ulcerative Colitis Associated with Cholangiocellular Carcinoma: A Case Report and Literature Review. *Ann Clin Case Rep.* 2017; 2: 1351.

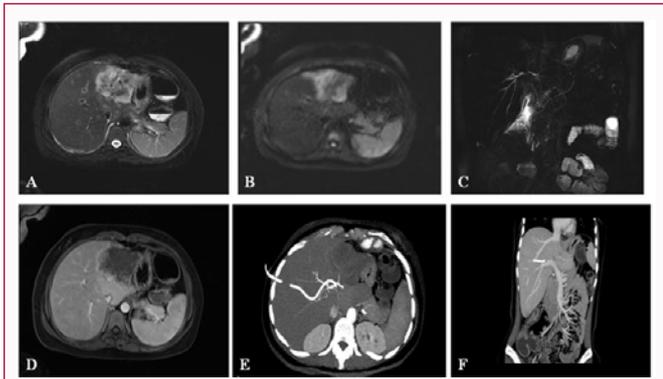
ISSN: 2474-1655

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### Case Presentation

#### General data

A 24-year-old female patient was admitted to Zhongshan hospital due to recurrent abnormal liver function over a period of 14 years and upper abdominal pain for over 1 month. She was treated with mesalazine after the diagnosis of UC in 1999. Several follow-up examinations revealed elevated Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), and  $\gamma$ -Glutamyl Transpeptidase (GGT). Specifically, ALP and GGT were elevated to 2–3-fold of the Upper Limit of Normal (ULN). During regular follow-ups, the patient did not report any symptoms of discomfort such as bloating or abdominal pain; no nausea, vomiting or anorexia; no fever, rash or xanthochromia of the skin and sclera. No further diagnosis or treatment was commenced. In 2009, her UC was well controlled and the dose of mesalazine was gradually reduced to withdrawal. Six months after withdrawal of mesalazine, repeat liver function tests showed elevated liver enzymes, especially ALP and GGT, which were 1–2-fold of ULN. The patient sought medical attention, but the subsequent liver biopsy did not reveal any obvious abnormalities. She was given intermittent, symptomatic treatment for liver dysfunction. In February 2015, the patient experienced postprandial upper abdominal pain. The patient denied acid reflux, belching, nausea, vomiting, diarrhea, fever, rash, jaundice, joint pain and other discomforts. She visited a local hospital and liver function tests showed: total bilirubin 21  $\mu\text{mol/L}$ , conjugated bilirubin 14  $\mu\text{mol/L}$ , albumin 42 g/l, ALT 117 IU/l, AST 131 IU/l and ALP 962 IU/l. She tested negative for hepatitis A, B, C and E viral markers. Gastroscopy showed superficial gastritis, polypoid bulge, and erosion in the gastric antrum, and cardiac polyp (most likely inflammatory). Gastric antral mucosal biopsy showed severe active chronic superficial inflammation with mucosal erosion. Abdominal ultrasound showed hepatomegaly, diffuse liver lesion, hypoechoic mass in the left hepatic lobe, and gallbladder wall edema. Abdominal contrast-enhanced CT showed focal liver lesions, suspicious for neoplastic lesions, likely atypical hemangioma or bile-duct-derived tumors. To clarify the nature



**Figure 1:** (A) Large liver lesion on the left hepatic lobe with in distinct boundary, measured approximately  $7.1 \times 5.1$  cm in size; heterogeneous high signal on T2-weighted imaging and (B) high signal on diffusion-weighted imaging; (C) MRCP revealed irregular intrahepatic bile duct stricture; (D) contrast-enhanced arterial phase lesions presented with peripheral irregular enhancement; (E,F) CTA of the hepatic artery and CTV of the portal vein, hepatic vein and hepatic artery indicated invasion of the left hepatic artery, left and middle hepatic veins, and left hepatic portal vein, with blurred boundaries.

of focal liver lesions, the patient was admitted to the Department of Gastroenterology of Zhongshan hospital. Since the onset of disease, she maintained a clear state of consciousness with normal mental health and appetite, sufficient sleep, normal urination and defecation, and denies significant weight fluctuation. The patient is allergic to cephalosporin. She denied a history of hepatitis, tobacco smoking or alcohol consumption, and toxicant exposure. She was single and has no children, and has a normal menstrual cycle. Her parents were in good health.

### Physical examination

Upon admission, her body temperature was  $36.8^{\circ}\text{C}$ , pulse rate was 78 beats/min, respiratory rate was 18 breaths/min, and blood pressure was  $110/78$  mmHg. She was conscious, mentally normal, physically active and cooperative upon examination. Her skin and sclera showed xanthochromia with no evident hemorrhagic spots, liver palm, or spider angioma. She had no palpable enlargement of superficial lymph nodes. The percussion and breath sounds of both lungs were clear. She had no precordial bulge and the border of cardiac dullness was within normal limits. Her heart rhythm was regular and no pathological murmurs were auscultated in the auscultatory sites. Her abdomen was flat and soft, with right upper quadrant tenderness but no rebound tenderness, muscle tension or abnormal mass. Her liver was palpable with one finger under the costal margins, while the spleen was not palpable. Her renal and hepatic regions were not sensitive to percussion. Shifting dullness was negative. Bowel sound frequency was 3 times/min. Neurological examination was negative. No pitting edema was observed on either lower extremities.

### Laboratory tests

Blood: erythrocyte count  $3.60 \times 10^{12}/\text{l}$ , hemoglobin 104 g/l, platelet count  $501 \times 10^9/\text{l}$ , leukocyte count  $9.67 \times 10^9/\text{l}$ , percentage of neutrophils 71.3%, percentage of lymphocytes 16.2%; erythrocyte sedimentation rate:  $>120$  mm/H. Urine: bilirubin ++, without any other abnormalities; stool: normal; fecal occult blood: negative. Liver function: total bilirubin  $64.4 \mu\text{mol}/\text{l}$ , direct bilirubin  $59.7 \mu\text{mol}/\text{l}$ , albumin 33 g/l, globulin 38 g/l, ALT 55 U/l, AST 61 U/l, ALP 561 U/l, GGT 382 U/l, lactate dehydrogenase 201 U/l, cholinesterase 4132 U/l, prealbumin 0.12 g/l; kidney function: urea 1.8 mmol/l, creatinine 39

$\mu\text{mol}/\text{l}$ , uric acid  $139 \mu\text{mol}/\text{l}$ . Coagulation: prothrombin time 12.2 s, international normalized ratio 1.05, activated partial thromboplastin time 36.5 s, D-dimer  $2.17 \text{ mg}/\text{l}$ . Tumor markers: carbohydrate antigen (CA)125  $451.3 \text{ IU}/\text{ml}$ ;  $\alpha$  fetoprotein, carcinoembryonic antigen, CA199 was within the normal range. Ferritin  $>2 \mu\text{g}/\text{ml}$ . Electrolyte and autoantibodies were within the normal range.

### Auxiliary examination

Upper abdominal contrast-enhanced magnetic resonance imaging (Figure 1) revealed a space-occupying lesions in the left hepatic lobe, with a tubercle in the caudal lobe involving blood vessels of the left lobe, suspicious for atypical hemangioma or bile duct Malignant Tumor (MT); other features included mild porta hepatitis lymphadenopathy and edema, as well as thickening of the gallbladder wall. Contrast-enhanced ultrasound for liver imaging showed multiple solid lesions in the left lobe, highly suspicious for MT (cholangiocyte-derived); embolization of the left portal vein; and porta hepatitis lymphadenopathy. Computed Tomographic Angiography (CTA) of the hepatic artery and Computed Tomography Venography (CTV) of the portal vein, hepatic vein and inferior vena cava revealed invasion of the left hepatic artery, left and middle hepatic veins, and left portal vein. Nuclear medicine imaging of systemic cancer by Positron Emission Tomography (PET)/CT indicated high suspicion for MT in the left lobe with intrahepatic metastasis, and porta hepatitis, retroperitoneal and thoracic lymph node metastases, as well as abdominal and pelvic implantation metastases, with a small amount of peritoneal fluid.

### Diagnosis and Treatment

The patient presented with progressive jaundice after admission. A Percutaneous Transhepatic Cholangial Drainage (PTCD) was performed on March 17, 2015. Intra-operative cholangiography revealed a slight right intrahepatic bile duct dilatation and irregular right hepatic duct stricture. Jaundice was alleviated following PTCD.

### Discussion

Inflammatory Bowel Disease (IBD) is an immune-mediated and non-specific inflammatory condition of the gastrointestinal tract characterized by repeated recurrence and chronicity, including UC and Crohn's disease. It is reported that 21–47% of IBD cases are associated with extra intestinal manifestations [1,2]. Extra intestinal manifestations involving the skin, eyes, and joints are often presented in parallel with disease activity of IBD, while hepatobiliary system diseases such as PSC, small-duct PSC, primary biliary cirrhosis, non-alcoholic fatty liver diseases, and cholelithiasis are inconsistent with IBD progression but generally occur independent of intestinal inflammation. PSC is an unexplained chronic cholestatic liver disease characterized by progressive inflammation, fibrosis and multiple stenosis of the intrahepatic and extrahepatic bile duct systems. PSC is currently well recognized as the most common hepatobiliary complication of IBD. The relationship between PSC and IBD has been reported mainly in Western countries. Up to 80% of PSC cases are associated with IBD in Northern Europe and the United States. The incidence of IBD–PSC is 50% in Southern Europe and 35% in Asia, reported mainly in Japan and Korea. Few studies have been reported in China, of which, recent reports on the incidence of IBD–PSC were single-center studies with small sample size. Despite large differences in the results, the incidence of IBD–PSC is significantly lower in China compared to that of Europe and the United States [3,4]. In other countries, 1.4–7.5% of IBD patients develop concomitant PSC

during disease progression, with a UC incidence of 2.0–7.5% and a CD incidence of 1.4–3.4% [5]. Similar results have been obtained by recent studies in China [6].

The pathogenesis of PSC-IBD remains unclear. From a microbiology viewpoint, IBD is diagnosed when permeability of the intestinal-mucosal barrier increases, allowing bacterial endotoxins and toxic cholic acids concentration to increase in the blood, then transported to the liver to activate Kupffer cells, triggering inflammatory mediators (eg. tumor necrosis factor), facilitating bile duct damage and hyperplasia resembling the pathological changes in PSC. This point of view is supported by the finding of intestinal bacilli in the portal veins of an animal model, although the exact pathogenesis remains unclear [7].

Significantly diverse clinical manifestations can be found in PSC, which may range from asymptomatic to recurrent episodes of jaundice, fatigue, anorexia, weight loss, abdominal pain, pruritus, hepatosplenomegaly, ascites, fever and diarrhea. Most PSC patients are asymptomatic upon diagnosis, but merely presents with elevation of serum ALP or other biochemical indices of hepatic function. Thus, PSC is easily over looked, leading to clinical misdiagnosis. Clinical awareness should be stressed in IBD patients with persistent abnormalities of liver function, especially those with persistent ALP elevation, for possible diagnosis of concomitant PSC. Current diagnosis of PSC is based primarily on imaging studies. Although Endoscopic Retrograde Cholangiopancreatography (ERCP) remains the gold standard [8] for diagnosis, its invasive nature can lead to serious complications. Owing to its non-invasiveness and ease of operation, Magnetic Resonance Cholangiography (MRCP) is increasingly used for diagnosis of PSC, with a sensitivity of 80% and specificity of 90% [9]. The typical pathological feature of PSC is the “onion-skin” type bile duct fibrosis. This pathological change can be used as the basis for diagnosis and determination of lesion severity. However, such pathological feature only applies to 10% of PSC patients, thus limits its diagnostic value. Research has shown that liver biopsy cannot provide additional diagnostic information for IBD patients after being examined by cholangiography [10]. Therefore, liver biopsy is not recommended for patients with typical lesions evident on cholangiography [11]. Liver biopsy needs to be further considered only when the diagnosis by ERCP is inconclusive. The patient reported in this study had a 14-years history of UC and previously treated with mesalazine for an extended period of time. During the course of disease, her liver function was repeatedly found to be abnormal, with prominent elevation of ALP and GGT, without obvious clinical manifestations. She was misdiagnosed with mesalazine-induced liver damage, without further relevant examinations. After admission to our hospital, MRCP showed irregular intrahepatic biliary stricture (Figure 1E and 1F). Cholangiography during PTCD showed right intrahepatic bile duct dilatation and irregular right hepatic duct stricture. No abnormalities was reported by the liver biopsy. However, as previously discussed, liver biopsy poses limitations and therefore, the patient was still considered to have UC with concomitant development of PSC.

PSC has a poor prognosis, with an average survival period of 9.6–18 years. The risk ratio of PSC associated with various malignant tumors is 13–14%; most commonly CCC (11%) followed by colorectal carcinoma (9%). Other concomitant malignancies include hepatocellular carcinoma, gallbladder carcinoma and pancreatic carcinoma [9]. Progression of PSC into CCC occurs mainly in patients

with history of IBD of over 15 years, or patients who have pancolitis, regardless of disease severity [12]. CCC-PSC is present in adolescents as well as adults [13]. After admission to our hospital, MRCP, contrast-enhanced ultrasound and PET-CT all suggested bile-duct-derived malignancy in our patient. Hence, she was considered to have developed concomitant PSC during the course of UC, which further progressed to CCC. Since the patient evident distant metastases, she was diagnosed with end-stage CCC.

Currently, there are no available treatment that can alter disease progression or the natural course of PSC. Studies have shown that low-dose ursodeoxycholic acid (UDCA; 13–15 mg/kg/day) has a positive role in improving liver function in patients with PSC, while high-dose UDCA (28 mg/kg/day-30 mg/kg/day) does not provide additional benefits [14]. Recent clinical follow-up studies with large samples have indicated that although UDCA can improve biochemical indices for PSC patients, it has no effect on liver histology and no significant impact on mortality, need for liver transplantation, and prognosis of CCC [15]. Endoscopic intervention and surgical procedures can alleviate biliary obstruction and reduce liver damage to a certain extent, however, liver transplantation is still preferred for end-stage PSC or CCC-PSC. Liver transplantation is the only effective treatment, with 5- and 10-year survival rates of 85% and 70% post-transplantation, respectively. Unfortunately, our patient had distant metastases and liver transplantation was contraindicated, thus, only interventional therapy was applied to alleviate her symptoms.

AN Ananthakrishnan “et al.” [16] reported that patients with IBD-PSC had significantly increased overall risk of cancers including cholangiocarcinoma compared to patients without PSC. Tsuchiya “et al.” [17] reported a case of concomitant colitic cancer and intrahepatic cholangiocarcinoma in a patient with history of UC recently. Clinicians should be aware of the disease and closely monitor UC patients who repeatedly have abnormal liver function test results. Specifically, in patients with persistent ALP elevation, MRCP or ERCP should be employed to clarify diagnosis and provide timely intervention when necessary.

## Research Funding

National Natural Science Foundation of China (No. 81370549).

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