World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i26.3171

World J Gastroenterol 2011 July 14; 17(26): 3171-3172
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Gut-liver axis plays a role in hepatocarcinogenesis of patients with Crohn's disease

Shu-Mei Zheng, De-Jun Cui, Qin Ouyang

Shu-Mei Zheng, De-Jun Cui, Qin Ouyang, Department of Gastroenterology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China
Author contributions: Zheng SM wrote the Letter; Cui DJ collected the relevant literature; Ouyang Q revised the letter.
Correspondence to: Qin Ouyang, Professor, Department of Gastroenterology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China. qinouyang3@163.com
Telephone: +86-28-85422387 Fax: +86-28-85422389
Received: January 30, 2011 Revised: March 25, 2011
Accepted: April 2, 2011
Published online: July 14, 2011

Abstract

The development of hepatocellular carcinoma (HCC) is attributed to several factors, including chronic viral infection, alcohol consumption, exposure to aflatoxin B1 and metabolic disorders. Several recent reports have shown that HCC can occur in patients with long-standing Crohn's disease (CD) in the absence of other underlying high-risk liver diseases. There may be an association between CD and hepatocarcinogenesis, however, the precise mechanism for this requires further investigations.

Key words: Inflammatory bowel disease; Crohn's disease; Hepatocellular carcinoma; Intestinal flora; Azathioprine; Enterohepatic circulation

Peer reviewer: Heitor Rosa, Professor, Department of Gastroenterology and Hepatology, Federal University School of Medicine, Rua 126 n.21, Goiania - GO 74093-080, Brazil

Zheng SM, Cui DJ, Ouyang Q. Gut-liver axis plays a role in hepatocarcinogenesis of patients with Crohn's disease. *World J Gastroenterol* 2011; 17(26): 3171-3172 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i26/3171.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i26.3171

TO THE EDITOR

We have read with great interest the article by Ishida *et al*[1], which was recently published in *World J Gastroenterology*, issue No. 25, 2010. The authors reported a case of hepatocellular carcinoma (HCC) that occurred in a patient with Crohn's disease (CD) in the absence of chronic hepatitis or liver cirrhosis. This suggested that Azathioprine treatment could be related to hepatocarcinogenesis in CD patients. Upon reading this interesting case report, we wondered whether the risk factor for the development of HCC in the setting of CD was CD itself or its treatment.

Azathioprine is currently the most common immunosuppressive drug for the treatment of inflammatory bowel disease (IBD), particularly for maintaining the remission of the patients with a complex clinical course. There is little doubt that, once this drug is indicated, its treatment should be continued for an extended period of time. Whether or not immunosuppressive therapy increases the risk of malignancy in IBD patients is controversial. Although the prolonged use of Azathioprine is considered theoretically to increase the occurrence of cancer, studies aimed at elucidating the risk of neoplasia in IBD patients treated with Azathioprine have concluded that Azathioprine does not substantially increase the risk of cancer development[2-4]. A global consensus about the association between immunosuppressants and malignancies has suggested a favorable risk/benefit ratio in the long-term use of Azathioprine[5].

Although the causes of IBD remain incompletely understood, the prevailing consensus is that the intestinal flora drives an unmitigated intestinal immune response and inflammation in the genetically susceptible host. CD is considered to be a systemic disorder that often involves multiple organs including the gastrointestinal tract. A meta-analysis[6] that assessed the relative risk of all types of cancers occurring outside the gastrointestinal tract found an increased risk in CD patients; and a potential correlation between long-standing CD and the development of HCC may therefore exist. A recent study[7]

revealed an intimate cross-talk between gut microbes, the lower bowel and liver in the evolution of HCC, and demonstrated that gut microbes could promote HCC. Several mechanisms could be involved. Firstly, bacteria may alter the colonic mucosal integrity and/or receptor activation, permitting the passive or facilitated the entry of harmful bacteria or their products into the circulation. Secondly, the microbial colonization of the bowel may invoke the release of numerous cytokines from the intestine and/or mesenteric lymph nodes that act upon the liver. Finally, intestinal bacteria may disrupt enterohepatic feedback loops, such as those associated with bile acid recirculation.

Recently, enterohepatic *Helicobacter* species, such as *H. hepaticus*, *H. bilis*, *Helicobacter sp. flexispira* and *H. cinaedi*, which belong to a rare phyla of luminal flora, have been identified in the lower intestinal and biliary tract of animals, and their overgrowth may cause chronic inflammatory bowel and liver diseases in rodents, poultry and primates. These bacteria have also been implicated in gastroenteritis, cholecystitis and certain liver diseases, including HCC in humans[8-11]. Several clinical observations have indicated that the modulation of the gut-liver axis using probiotics may play a therapeutic role, especially in the pathophysiological conditions where intestinal microflora may be involved as a cofactor of chronic liver damage.

In summary, it is possible that several factors related to CD may directly or indirectly affect the development of HCC in patients with CD. We consider that altered gut microbes would more likely disrupt enterohepatic homeostasis and promote the development of liver cancer than medication. A study of cumulative cases and further researches may unmask the intestinal bacteria that are associated with the increased risk of HCC in humans. Such microbes may represent attractive therapeutic targets.

REFERENCES

1 **Ishida M**, Naka S, Shiomi H, Tsujikawa T, Andoh A, Nakahara T, Saito Y, Kurumi Y, Takikita-Suzuki M, Kojima F, Hotta M, Tani T, Fujiyama Y, Okabe H. Hepatocellular carcinoma occurring in a Crohn's disease patient. *World J Gastroenterol* 2010; **16**: 3215-3218

2 **Masunaga Y**, Ohno K, Ogawa R, Hashiguchi M, Echizen H, Ogata H. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. *Ann Pharmacother* 2007; **41**: 21-28

3 **Fraser AG**, Orchard TR, Robinson EM, Jewell DP. Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. *Aliment Pharmacol Ther* 2002; **16**: 1225-1232

4 **Connell WR**, Kamm MA, Dickson M, Balkwill AM, Ritchie JK, Lennard-Jones JE. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. *Lancet* 1994; **343**: 1249-1252

5 **Etchevers MJ**, Aceituno M, Sans M. Are we giving azathioprine too late? The case for early immunomodulation in inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 5512-5518

6 **von Roon AC**, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The risk of cancer in patients with Crohn's disease. *Dis Colon Rectum* 2007; **50**: 839-855

7 **Fox JG**, Feng Y, Theve EJ, Raczynski AR, Fiala JL, Doernte AL, Williams M, McFaline JL, Essigmann JM, Schauer DB, Tannenbaum SR, Dedon PC, Weinman SA, Lemon SM, Fry RC, Rogers AB. Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens. *Gut* 2010; **59**: 88-97

8 **Fox JG**. The non-H pylori helicobacters: their expanding role in gastrointestinal and systemic diseases. *Gut* 2002; **50**: 273-283

9 **Solnick JV**, Schauer DB. Emergence of diverse Helicobacter species in the pathogenesis of gastric and enterohepatic diseases. *Clin Microbiol Rev* 2001; **14**: 59-97

10 **Fox JG**, Schauer DB, Wadstr¨om T. Enterohepatic Helicobacters spp. *Curr Opin Gastroenterol* 2001; **17** (suppl 1): S28-S31

11 **Abu Al-Soud W**, Stenram U, Ljungh A, Tranberg KG, Nilsson HO, Wadström T. DNA of Helicobacter spp. and common gut bacteria in primary liver carcinoma. *Dig Liver Dis* 2008; **40**: 126-131

S- Editor Sun H **L- Editor** Ma JY **E- Editor** Ma WH