

Hepatoma and trematode infestation: a short review

Viroj Wiwanitkit^{1,2,3,4,5}

¹Department of Tropical Medicine, Hainan Medical University, Haikou 571199, Hainan, China

²Department of Medicine, Faculty of Medicine, University of Nis, 18000 Nis, Serbia

³Department of Biological Science, Joseph Ayobabalola University, Ikeji-Arakeji 233121, Nigeria

⁴Department of Community Medicine, Dr. DY Patil Medical University, Pune 411018, Maharashtra, India

⁵Public Health Curriculum, Surin Rajabhat University, Surin 32000, Thailand

ABSTRACT

Hepatoma is a common cancer that can be seen around the world and clinical correlation between infection and hepatoma is evident. Hepatitis virus infection is proved for its relationship with hepatoma. However, the knowledge of other infections is still limited. In this short review, the relationship between hepatoma and some trematode infestation including echinococcosis fascioliasis, opisthorchiasis, clonorchiasis and schistosomiasis are described and discussed. Opisthorchiasis and clonorchiasis are confirmed for cholangiocarcinoma carcinogenesis but still lack evidence for hepatoma carcinogenesis. Schistosomiasis can increase the severity of hepatoma.

Key words: Hepatoma; infestation; trematode

Address for correspondence:

Prof. Viroj Wiwanitkit, Public Health Curriculum, Surin Rajabhat University, Surin 32000, Thailand. E-mail: wviroj@yahoo.com

Received: 10-03-2015, **Accepted:** 01-06-2015

INTRODUCTION

Hepatoma is a common malignancy seen around the world. The clinical correlation between infection and hepatoma is very interesting. Relationship between hepatitis virus infection and hepatoma is confirmed. Chronic hepatitis B and chronic hepatitis C infections can result in hepatoma carcinogenesis. However, the knowledge on other infections is still limited. Many tropical infections have been continuously studied for the relationship with hepatoma. Here, the authors summarize and present the information on hepatoma and trematode infestation.

HEPATOMA AND ECHINOCOCCOSIS

Echinococcosis is a parasitic infestation primarily observed in

liver (in humans), which is associated with liver cystic disorder called hydatid cyst. Previous reports indicate a positive correlation between liver hydatid cyst and hepatoma.^[1-6] Although it is rare, hydatid disease needs to be included in differential diagnosis of hepatoma.^[7,8] Hoffmann *et al.*^[7] noted that the final diagnosis could be derived only if the histopathological examination is done. At present, it is accepted that the co-incidence between hydatid disease and hepatoma is possible, however, there is still no conclusion on the carcinogenesis process due to hydatid disease. Kübeck *et al.*^[6] recently noted that some authors considered echinococcosis as a trigger for hepatoma and suggested for further study on such relationship. In fact, hydatid disease has a role in causing liver fibrosis and cirrhosis,^[9] which is a precancerous liver lesion. However, the lesion due to hepatic cyst and fibrosis is usually severe. The patient should not have a long survival to have a fully developed hepatoma as a consequence.

HEPATOMA AND FASCIOLIASIS

Fascioliasis is another common human parasitic infestation.^[10] The relationship between fascioliasis and biliary cirrhosis is speculated in some publications. Vítovec^[11] mentioned for the role of biliary cirrhosis of fasciolar origin

Access this article online	
Website: http://www.hrjournal.net/	Quick Response Code 
DOI: 10.4103/2394-5079.158390	

on the hepatoma carcinogenesis is cattle. However, this is not the finding in human beings. Kabaalioglu *et al.*^[12] studied on human fascioliasis and concluded that “long-term complications are rare in fascioliasis, and malignancy or cirrhosis related to the disease has not been observed.”

HEPATOMA AND OPISTHORCHIASIS

Liver fluke infestation or opisthorchiasis is another important parasitic infestation. It is common in Indochina and has been proved for its relationship in the occurrence of cholangiocarcinoma.^[13] However, the role of opisthorchiasis on hepatoma carcinogenesis is still not conclusive at present. There are some reports on co-incidences between opisthorchiasis and hepatoma.^[14,15] Nevertheless, the epidemiological investigation still reveals no clear evidence that opisthorchiasis can induce hepatoma carcinogenesis. Suksumek *et al.*^[16] recently studied *Opisthorchis viverrini* DNA in patients with hepatocellular carcinoma (HCC) and found that the presence of parasite had no relationship to any cancer. In fact, the finding by Suksumek *et al.*^[16] is not surprising since the main mechanism of cholangiocarcinoma carcinogenesis is due to chronic biliary tract irritation by parasitic infestation. Since the *O. viverrini* does not infest in hepatic parenchyma, the induction of the HCC should not occur.

HEPATOMA AND CLONORCHIASIS

Similar to opisthorchiasis, clonorchiasis is known for its relationship with cholangiocarcinoma carcinogenesis.^[17] The mechanism is the same as that described in opisthorchiasis model. For hepatoma, there are some reports on the co-incidence between clonorchiasis and hepatoma.^[18] However, the role of clonorchiasis in hepatoma carcinogenesis is still controversial. A recent report by Tan *et al.*^[19] concluded that clonorchiasis could be an important risk factor for hepatoma. When the course of clonorchiasis is prolonged, the risk of hepatoma could increase.^[19] Hepatitis B virus (HBV) infection, alcohol consumption, and clonorchiasis might have synergistic actions in the development of hepatoma.^[19] Chen *et al.*^[20] found that excretory/secretory products of the parasite might play an important role in hepatoma carcinogenesis. However, the study reported by Chen *et al.*^[20] is only an *in vitro* study. Chen *et al.*^[20] noted that “Csseverin”, an important excretory/secretory product, might exacerbate hepatoma carcinogenesis, however, this is only a speculation at this point.

HEPATOMA AND SCHISTOSOMIASIS

The role of schistosomiasis on hepatoma carcinogenesis is widely discussed. In animals, liver cirrhosis due to infestation

can induce hepatoma carcinogenesis.^[21,22] In humans, there are some reports on positive correlation between schistosomiasis and hepatoma.^[23-32] Since the induction of liver fibrosis in human due to schistosomiasis is observed, it is proposed that this pathology can be the underlying cause of hepatoma which may occur in future.^[25-27] In a case-control study by Khella *et al.*,^[26] it was found that the history of schistosomiasis is significantly different between case and control. A similar observation was also reported by el-Zayadi *et al.*^[31] Badawi and Michael^[30] found that schistosomiasis increased the severity of HBV infection and elevated the risk of HCC associated with the HBV infection. However, Nakashima *et al.*^[24] studied necropsies with hepatoma coincident with schistosomiasis, and concluded that chronic schistosomiasis, on its own, is unlikely to be the cause of primary liver cell carcinoma. Nakashima *et al.*^[32] also reported that HCC related to viral hepatitis B and/or C also increased in cases with underlying schistosomiasis. Yosry^[33] concluded that there is inadequate evidence for the carcinogenicity of *Schistosoma mansoni* in humans. *S. mansoni* may still be linked to HCC through potentiating effects of HBV and hepatitis C virus (HCV) on the liver. El-Tonsy *et al.*^[34] concluded that schistosomiasis accelerates hepatic dysplastic changes in the presence of other risk factors making cancer appear early and with a more aggressive nature, compared to the same risk in absence of schistosomiasis. Therefore, it can be summarized that superimposing the effects of HBV and HCV on the liver can be expected in the cases with combined schistosomiasis and hepatitis virus infection.^[33]

Conclusively, schistosomiasis can induce liver fibrosis, which is a precancerous lesion. In addition, chronic schistosomiasis is common. The increased argyrophilic nucleolar organizer regions proteins which related to increased dysplasia can be observed in the chronic schistosomiasis.^[35] In addition, new observation on the deteriorating immunological status in chronic schistosomiasis is also reported.^[36] Dysregulation of cellular immune responses, impaired T-lymphocytes and natural killer cells, can be seen in the patients and can ease the occurrence of cancer.^[36] The poor immunity is said to be partially due to the poor nutritional status,^[37] which is a common complication in chronic schistosomiasis.^[38] Hence, it is no doubt that schistosomiasis can be the cause of hepatoma carcinogenesis. Focusing on the case with combined chronic schistosomiasis and chronic hepatitis B or hepatitis C infection, a more severe liver pathology can be expected. The precancerous liver pathological change due to hepatitis virus can be superimposed by liver fibrosis induced by schistosomiasis and this should be the explanation for finding that schistosomiasis increase the severity of hepatitis related hepatoma.

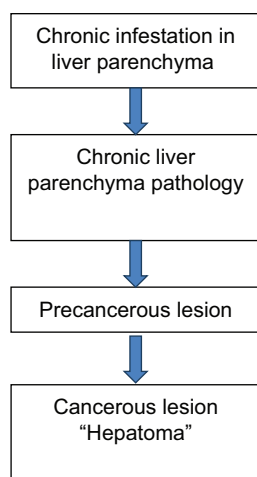


Figure 1: Common mechanism that trematode can induce hepatoma carcinogenesis

CONCLUSION

There are many reports on hepatoma and trematode infestation. Opisthorchiasis and clonorchiasis are confirmed for cholangiocarcinoma carcinogenesis, but there is still lack for the evidence on hepatoma carcinogenesis. For schistosomiasis, it is found that schistosomiasis increase the severity of hepatitis related hepatoma. Focusing on the mechanism, the trematode that has a possible role in hepatoma carcinogenesis usually has a chronic form of infestation. The chronic liver parenchyma pathology, especially for liver fibrosis and cirrhosis, is the main precancerous lesion that can further develop into hepatoma [Figure 1].

REFERENCES

- Bourne MS, Williams GE. Compression of the inferior vena cava by hydatid disease of the liver with associated hepatocellular carcinoma. *Gastroenterology* 1963;45:667-9.
- Perrone-Donnorso R. Double peritoneal dissemination of hydatidosis and concomitant hepatocellular carcinoma. *Riv Anat Patol Oncol* 1969;35:266-80. (in Italian)
- Zöld E, Barta Z, Zeher M. Hydatid disease of the liver and associated hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2005;3:xxxv.
- Kato T, Seino Y, Takada K, Maruya M, Okubo S, Nakamura H, Inoue Y, Meguro T, Horita S, Oshikiri T, Yamada H, Miyasaka Y, Fujita M, Morita T, Yoshida T, Chikai K. A resectable case of hepatocellular carcinoma complicated with hepatic alveolar echinococcosis. *Nihon Shokakibyo Gakkai Zasshi* 2003;100:587-92. (in Japanese)
- Kostov D, Dragnev N, Patanov R, Kobakov G. Hepatocellular carcinoma complicated with echinococcal cyst of the liver. *Khirurgiia (Sofia)* 2010;(4-5):49-50. (in Bulgarian)
- Kübeck M, Stöckl V, Stainer W, Schermaier T, Preisinger J, Schauer W, Hochleitner U, Höbling W, Barth TF, Stadler B, Knoflach P, Kirchgatterer A. Cystic echinococcosis and hepatocellular carcinoma – a coincidence? A case report. *Z Gastroenterol* 2014;52:657-62. (in German)
- Hoffmann T, Schlensak M, Erhard J, Trenn G. Echinococcosis – A rare differential diagnosis of a tumorous hepatic lesion. *Z Gastroenterol* 2003;41:913-6. (in German)
- Kohlenberg A, Wüsten O, Dierkes C, Discher T, Tappe D. Education and Imaging. Hepatobiliary and pancreatic: alveolar echinococcosis mimicking hepatocellular carcinoma. *J Gastroenterol Hepatol* 2010;25:1712.
- Stoianov G, Iarūmov N, Damianov N, Ilieva IU. Liver cirrhosis caused by liver echinococcosis. *Khirurgiia (Sofia)* 2006;(3):20-2. (in Bulgarian)
- Mas-Coma S, Valero MA, Bargues MD. Fascioliasis. *Adv Exp Med Biol* 2014;766:77-114.
- Vítovec J. Hepatocellular carcinoma in cattle and its relationship to biliary cirrhosis of fasciolar origin. *Vet Pathol* 1974;11:548-57. (in German)
- Kabaalioglu A, Ceken K, Alimoglu E, Saba R, Cubuk M, Arslan G, Apaydin A. Hepatobiliary fascioliasis: sonographic and CT findings in 87 patients during the initial phase and long-term follow-up. *AJR Am J Roentgenol* 2007;189:824-8.
- Kim YI. Liver carcinoma and liver fluke infection. *Arzneimittelforschung* 1984;34:1121-6.
- Sonakul D, Koopirochana C, Chinda K, Stitnimakarn T. Hepatic carcinoma with opisthorchiasis. *Southeast Asian J Trop Med Public Health* 1978;9:215-9.
- Srivatanakul P, Parkin DM, Jiang YZ, Khlat M, Kao-Ian UT, Sontipong S, Wild C. The role of infection by *Opisthorchis viverrini*, hepatitis B virus, and aflatoxin exposure in the etiology of liver cancer in Thailand. A correlation study. *Cancer* 1991;68:2411-7.
- Suksunek N, Leelawat K, Leelawat S, Russell B, Lek-Uthai U. TaqMan real-time PCR assay for specific detection of *Opisthorchis viverrini* DNA in Thai patients with hepatocellular carcinoma and cholangiocarcinoma. *Exp Parasitol* 2008;119:217-24.
- Purtilo DT. Clonorchiasis and hepatic neoplasms. *Trop Geogr Med* 1976;28:21-7.
- Nakashima T, Sakamoto K, Okuda K. A minute hepatocellular carcinoma found in a liver with clonorchis sinensis infection: report of two cases. *Cancer* 1977;39:1306-11.
- Tan SK, Qiu XQ, Yu HP, Zeng XY, Zhao YN, Hu L. Evaluation of the risk of clonorchiasis inducing primary hepatocellular carcinoma. *Zhonghua Gan Zang Bing Za Zhi* 2008;16:114-6. (in Chinese)
- Chen X, Li S, He L, Wang X, Liang P, Chen W, Bian M, Ren M, Lin J, Liang C, Xu J, Wu Z, Li X, Huang Y, Yu X. Molecular characterization of severin from *Clonorchis sinensis* excretory/secretory products and its potential anti-apoptotic role in hepatocarcinoma PLC cells. *PLoS Negl Trop Dis* 2013;7:e2606.
- Domingo EO, Warren KS, Stenger RJ. Increased incidence of hepatoma in mice with chronic schistosomiasis mansoni treated with a carcinogen. *Am J Pathol* 1967;51:307-21.
- Abe K, Kagei N, Teramura Y, Ejima H. Hepatocellular carcinoma associated with chronic *Schistosoma mansoni* infection in a chimpanzee. *J Med Primatol* 1993;22:237-9.
- Edington GM. Schistosomiasis and primary liver cell carcinoma. *Trans R Soc Trop Med Hyg* 1979;73:351.
- Nakashima T, Okuda K, Kojiro M, Sakamoto K, Kubo Y. Primary liver cancer coincident with *Schistosomiasis japonica*. A study of 24 necropsies. *Cancer* 1975;36:1483-9.
- Fujimoto H, Araki T, Hihara T, Karikomi M, Kachi K, Saito Y, Hayashi S, Uchiyama G. Hepatocellular carcinoma associated with *Schistosomiasis japonica*; CT and angiographic features. *Nihon Igaku Hoshasen Gakkai Zasshi* 1989;49:139-45. (in Japanese)
- Khella AK, Faris L, Helmy S, Yousif A, Esmail S. A hospital based case-control study of hepatocellular carcinoma. *J Egypt Public Health Assoc* 1992;67:249-58.
- Abdel-Hamid NM. Recent insights on risk factors of hepatocellular carcinoma. *World J Hepatol* 2009;1:3-7.
- Li ZJ, Luo DD, Dai JZ, Zheng LL, Wang XH, Liu SC, Shong GF, Yang YX, Wang HC. Immunohistochemical detection of HBsAg and HBeAg in the liver of patients with *Schistosomiasis japonica* complicated by hepatocellular carcinoma. *J Tongji Med Univ* 1991;11:141-4.
- Uetsuji S, Yamamura M, Okuda Y, Yamamichi K, Yamamoto M. Primary

- liver cancer coincident with *Schistosomiasis japonica*. *Gan No Rinsho* 1990;36:521-5. (in Japanese)
30. Badawi AF, Michael MS. Risk factors for hepatocellular carcinoma in Egypt: the role of hepatitis-B viral infection and schistosomiasis. *Anticancer Res* 1999;19:4565-9.
 31. el-Zayadi AR, Badran HM, Barakat EM, Attia Mel-D, Shawky S, Mohamed MK, Selim O, Saeid A. Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol* 2005;11:5193-8.
 32. Nakashima T, Kage M, Hirata M. A historical view of *Schistosomiasis japonica* in the Chikugo river basin. What can we learn from autopsies? *Parasitol Int* 2003;52:327-34.
 33. Yosry A. Schistosomiasis and neoplasia. *Contrib Microbiol* 2006;13:81-100.
 34. El-Tonsy MM, Hussein HM, Helal Tel-S, Tawfik RA, Koriem KM, Hussein HM. *Schistosoma mansoni* infection: is it a risk factor for development of hepatocellular carcinoma? *Acta Trop* 2013;128:542-7.
 35. Attallah AM, Tabll AA, El-Nashar E, El-Bakry KA, El-Sadany M, Ibrahim T, El-Dosoky I. AgNORs count and DNA ploidy in liver biopsies from patients with schistosomal liver cirrhosis and hepatocellular carcinoma. *Clin Biochem* 2009;42:1616-20.
 36. Attallah AM, Tabll AA, El-Sadany M, Ibrahim TA, El-Dosoky I. Dysregulation of blood lymphocyte subsets and natural killer cells in schistosomal liver cirrhosis and hepatocellular carcinoma. *Clin Exp Med* 2003;3:181-5.
 37. McGarvey ST, Aligui G, Graham KK, Peters P, Olds GR, Olveda R. *Schistosomiasis japonica* and childhood nutritional status in northeastern Leyte, the Philippines: a randomized trial of praziquantel versus placebo. *Am J Trop Med Hyg* 1996;54:498-502.
 38. Wahib AA, Masoud AA, Halem AA, Haseeb AN, Hassan AR, Darwish MA, Hegazi M, Abdallah KF. Cell mediated immune response in chronic liver diseases: schistosomal, viral and neoplastic. *J Egypt Soc Parasitol* 1998;28:929-39.

How to cite this article: Wiwanitkit V. Hepatoma and trematode infestation: a short review. *Hepatoma Res* 2015;1:63-6.

Source of Support: Nil. **Conflict of Interest:** None declared.