Is there a Role for Helicobacter Species in the Pathogenesis of

Hepatocellular Carcinoma in the Egyptian Patients

THESIS

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List of Abbreviations

AFP .....Alpha fetoprotein

AIDS……Acquired immune deficiency syndrome

C13.....Carbon 13

C14.....Carbon 14

CEA.....Carcino embryonic antigen

CT .....Computerized tomography

DNA.....Deoxyribonucleic acid

EHS…….Enterohepatic species

FDA…….Food and drug administration

FU .....Fluorouracil

HAV…….Hepatitis A virus

HBV .....Hepatitis B virus

HCC…….Hepatocellular carcinoma

HCV .....Hepatitis C virus

HEV……..Hepatitis E virus

H.pylori…….Helicobacter pylori

IL……...Interleukin

MALT……..Mucosa associated lymphoid tissue

MRI……..Magnetic resonance image

PAF……..Platelet activating factor

PCR……..Polymerase chain reaction

RNA…….Ribonucleic acid

TLR……..Toll like receptor

TNF……..Tumour necrosing factor

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INTRODUCTION

Infection by viruses and parasites can induce chronic inflammation that is a recognized risk factor for cancer (Avenaud et al., 2000). Hepatitis B and C viral infections, which induce chronic active hepatitis, are major risk factors for hepatocellular carcinoma (HCC). Infection of the liver by liver flukes also increases the risk of cancer (IARC, 1994).

Bacteria have been linked to cancer. The human gastric pathogen Helicobacter pylori induces a persistent infection that is considered to be a type I carcinogen because of its role in the development of gastric carcinoma (Forman et al., 1994; and Dunn et al.,1997) and gastric mucosa-associated lymphoid tissue lymphoma (Parsonnet et al., 1994). Other Helicobacter species have been identified in the intestinal tract, liver, and bile ducts of animals, and have been found to play a pathological role in enterohepatic diseases in animals and humans (Solnick and Schauer, 2001). Helicobacter hepaticus has been reported to be an agent that cause hepatic cancer in rodents. Recently, several separate research groups detected such Helicobacter organisms as H. pylori, H.pillorum, H. bilis, and Helicobacter species flexispira in the bile , gall bladder, or liver tissue of patients with primary sclerosing cholangitis, primary biliary cirrhosis, or primary liver carcinoma (Fox et al., 1998; and Wadstrom, 2000). These reports suggested that helicobacter organisms, including H. pylori, may play a role in the development of hepatobiliary diseases in humans , similar to the role that they play in animals.

HCC is one of the most common human cancers in the world. HCC ranks fifth among all cancers, and rate of incidence vary considerably by area or by country (Fan et al., 2002). Those regions where the risk for HCC is high are sub-Saharan Africa, China, and Southeast Asia (Kew , 2002). Although dietary exposure to aflatoxin B1 is one of the major risk factors for HCC, chronic infection with hepatitis B and C viruses are the most important risk factors for HCC worldwide (Fan et al.,2002) and in Egypt (Mohamed et al., 2000). Hereditary haemochromatosis and cirrhosis of almost any cause are also important risk factors (Fan et al.,2002) . Recently, several reports suggested that Helicobacter species may play a role in the development of HCC (waldstrom,2000)

AIM OF THE WORK :

This study initiated to find out whether Helicobacter species could be identified in the hepatic tissue of Egyptian patients with primary liver carcinoma and may have role in the pathogenesis of this disease.

PATIENTS AND METHODS

Twenty patients presented to Ain Shams University Hospital with hepatic focal lesion and planned to have partial hepatic resection as a treatment for the tumor and another twenty patients (control) who will have liver biopsy for other pathology than HCC, will undergo the following:

*Full history and clinical examination.

*Complete blood picture.

*Complete liver profile.

*Kidney function tests.

*Alphafetoprotein level.

*HBsAg.

*HCV Abs.

*Abdominal ultrasonography.

*Triphasic abdominal CT.

*Liver biopsy examination

Liver biopsies will be taken from the tumor tissue during partial hepatic resection and non-neoplastic tissue (control group). All specimens will be processed for:

*Routine histopathological examination.

*Modified Giemsa stain to search for Helicobacter bacteria.

Part of the liver biopsies will undergo rapid urease test to detect H. bacteria.

Hepatocellular carcinoma

Introduction

Hepatocellular cancer is one of the most common cancers in the world. It is also one of the most deadly, with a 5-year survival rate of less than 5% without treatment. Any chronic inflammatory liver disease has the potential to induce hepatocellular carcinoma, but the pathophysiologic process most commonly associated with the disease is cirrhosis, found in up to 80% of cases (*Flickinger et al., 1997*). Whether cirrhosis itself or the mechanism underlying cirrhosis is responsible for malignant transformation of hepatocytes is not known (*Flickinger et al., 1997*).

Certain viral, environmental, and hereditary causes of cirrhosis have a strong correlation with hepatocellular carcinoma. Chronic viral hepatitis as a cause of cirrhosis and hepatocellular carcinoma is well known. Hepatitis B virus infection is the leading cause of chronic liver disease and hepatocellular carcinoma around the world. *(VanDamme et al., 1997).* In the United States, hepatitis B virus infects about 1.2 million people and hepatitis C virus about 4 million people (*Gross et al ., 1998)*. Hepatitis C virus RNA is found in about 65% of patients who test negative for hepatitis B surface antigen at diagnosis of their hepatocellular carcinoma (*Dana et al., 1994).*

Alcohol use is also a common cause of cirrhosis, which can indirectly lead to hepatocellular carcinoma. However, a direct carcinogenic effect of alcohol on the liver has not been proved (*Akriviadis et al., 1998)*