Hepatocellular Carcinoma Pathogenesis, Clinical Presentation, And New Modalities of Management In Between Viral and Non-Viral Hepatitis

Essay

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Summary

Hepatocellular carcinoma (HCC) is one of the most common internal malignancies worldwide. It is the fifth most common cancer and the third cause of cancer-related death worldwide.

The incidence of HCC varies widely according to geographic location, with high incidence in sub-Saharan Africa and South East Asia.

Mostly, HCC arises in the setting of chronic liver disease, usually cirrhosis, HCC arising in a previously normal liver accounts for less than 10% of all HCCs.

The most frequent underlying cause of HCC is chronic hepatitis B, the next most common cause is hepatitis C. Other causes that predispose to HCC include alcoholic cirrhosis, NASH, aflatoxin BI and vinyl chloride exposure, hereditary hemochromatosis, α-1 antitrypsin deficiency, glycogen storage diseases and primary biliary cirrhosis.

Smoking, family history of HCC, and estrogen exposure are also implicated.

Most of the risk factors for HCC induce mutations in DNA and the genome, or facilitate the proliferation of hepatocytes and the fixation of DNA lesions. Different genetic alterations have been described in human HCC, including gain

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List of Abbreviations

^{13}C	Carbon isotope 13
^{90}Y	Yttrium-90
AASLD	The American Association for the Study of Liver Diseases
AFBI	Aflatoxin BI
AFP	Alpha Fetoprotein
AFP-L3	Fucosylated Isoform of AFP
AIDS	Acquired Immunodeficiency Syndrome
BCLC	The Barcelona Clinic Liver Cancer
CEUS	Contrast-enhanced Ultrasound
CHB	Chronic Hepatitis B
CI	Confidence Interval
CLIP	The Cancer of the Liver Italian Program
CT	Computed Tomography
D	Dimentional
DCP	Des-Gamma-Carboxy Prothrombin
DNA	Deoxyribonucleic Acid
FDG	2-[18F]fluoro-2-deoxy-D-glucose
FI	Fucosylation Index
HbeAg	Hepatitis B envelop Antigen
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBx	Hepatitis B Virus-encoded x
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HFE	Hereditary Hemochromatosis Gene
hTERT	Human Telomerase Reverse Transcriptase

IFN	Interferon
MDCT	Multidetector Computed Tomography
MELD	Model for end-stage Liver Disease
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
NASH	Nonalcoholic Steatohepatitis
PAI	Percutaneous Acetic acid Injection
PCR	Polymerase Chain Reaction
PEI	Percutaneous Ethanol Injection
PET	Positron Emission Tomography
PIVKA-II	Protein Induced by Vitamin K Absence or Antagonist II
RFA	Radiofrequency Ablation
RNA	Ribonucleic Acid
SPIO	Superparamagnetic Iron Oxide
T	Time
TACE	Transarterial Chemoembolization
TAE	Transarterial Embolization
TARE	Transarterial Radioembolization
TNM	Tumor-Node-Metastasis
UCSF	The University of California, San Francisco
UNOS	United Network for Organ Sharing
US	Ultrasound

Introduction

Hepatocellular carcinoma (HCC) accounts for 80% to 90% of primary liver cancer. It's a major health problem worldwide with an estimated incidence ranging between 500.000 and 1.000.000 new cases annually ***(Leong TY et al., 2005).***

The major risk factors include infection with hepatitis B or C virus, exposure to dietary aflatoxin BI (AFBI), vinyl chloride, alcohol consumption, smoking, and further inflammatory and oxyradical disorders including Wilson disease or hemochromatosis. α 1- antitrypsin deficiency, schistosomiasis, estrogen exposure, and membranous obstruction of inferior vena cava may also be implicated ***(David P. Kelsen et al., 2002).***

Many of the risk factors associated with HCC induce necroinflammatory liver disease, which, if allowed for many years, develops into cirrhosis and perhaps HCC. Recent studies have discovered genetic and epigenetic changes involved in the molecular pathogenesis of HCC, including somatic mutations in the p53 tumor suppressor gene. Other contributary mediators of HCC are metabolising enzymes which can either activate or detoxify these carcinogenic risk factors. Currently, many studies are trying to identify specific populations that may be at

risk for HCC based on their metabolic phenotypes ***(Frank Staib et al., 2003).***

Clinical presentation of HCC includes weakness, anorexia, weight loss, fever, abdominal pain, a large irregular liver, or an abdominal mass along with ascites. HCCs are vascular, and a bruit may be heard over the liver, or intraabdominal bleeding may occur ***(Liovet JM et al., 2003).***

The diagnosis of HCC is typically made by radiological liver imaging in combination with Alphafetoprotein (AFP). There's an agreement that biopsy proof of HCC is not required prior to surgery. Ultrasound is usually the first line investigation for patients with suspected HCC ***(David P. Kelsen et al., 2002).***

High resolution triphasic CT scan, MRI with contrast, and multislice CT are used to diagnose HCC and to assess tumor extent. Recently, superparamagnetic iron oxide-enhanced MRI may be used to differentiate well differentiated HCCs from dysplastic nodules, moderately differentiated, or poorly differentiated HCCs ***(Jeong- Min Lee et al., 2009).***

Indocyanine green fluorescent imaging enables the highly sensitive identification of small and grossly unidentifiable HCCs in real time, enhancing the accuracy of liver resection and operative staging ***(Takeshi Aoki et al., 2008).***

The diagnostic performance of AFP is inadequate, as it's only elevated in 40%- 60% of cases**.** Alternative serum biomarkers proposed candidates include telomerase ***(Oh BK et al., 2008),*** Glypican-3**.** Squamous cell carcinoma Antigen**,** PIVKAII, and Follistation ***(Gary Beale et al., 2008).***

For years, partial hepatectomy and liver transplantation have been considered as the main curative treatment for HCC. Currently, various local therapies are used, as local ablative therapy (radiofrequency ablation or percutaneous ethanol injection), Transarterial techniques (transarterial embolization, transarterial chemotherapy, transarterial chemo-embolization, transarterial radioembolization) and some forms of extracorporeal energy therapy ***(Lau WY, 2002).***

Other treatments include systemic doxorubicin, tyrosine kinase inhibitors, antiangiogenic agents, immunotherapy, and high- intensity focused ultrasound therapy ***(Masuzaki R et al., 2008).***

Aim of the Essay

An overview of HCC, epidemiology, pathogenesis, clinical presentation, recent methods of diagnosis, and new treatment modalities, in between viral and non-viral hepatitis.

Epidemiology and Risk Factors of Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most common internal malignancies worldwide. It is the fifth most common cancer and the third cause of cancer-related death worldwide ***(Zhao J et al., 2011)***. HCC accounts for up to 1 million deaths a year and is the third leading cause of cancer deaths worldwide ***(Philips GM et al., 2011)***.

For all patients, the 1-, 2-, and 3-year HCC-specific survival rates were 66.5 ± 5.3%, 52.3 ± 5.9%, and 39.1 ± 6.5% respectively, for the elderly and 66.7 ± 3.2%, 51.7 ± 3.5%, and 40.3 ± 3.6% respectively, for the young age group ***(Kozyreva ON et al., 2011)***.

Geographic Distribution

The incidence of HCC varies widely according to geographic location. The distribution of HCC also differs among ethnic groups within the same country, and between regions within the same country ***(Jemal A et al., 2011)***.

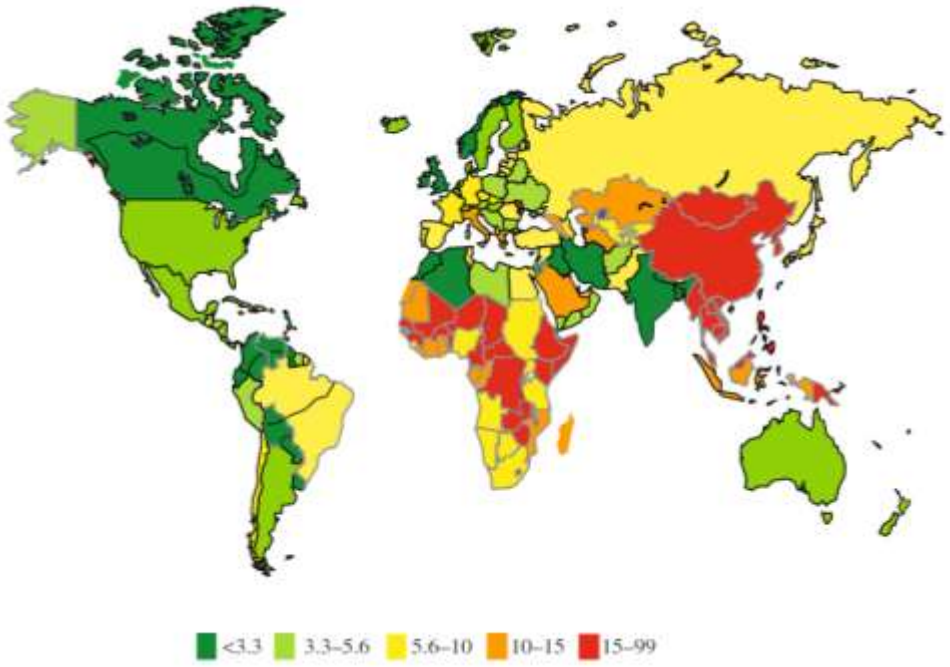

Fig. (1): Regional variations in the incidence rates of hepatocellular carcinoma categorized by age-adjusted incidence rates ***(White DL et al., 2010)***.

High incidence regions (more than 15 cases per 100,000 population per year) include sub-Saharan Africa, the People's Republic of China, Hong Kong, and Taiwan. The incidence is 24.2/100,000 in parts of Africa, and the 35.5/100,000 seen in Eastern Asia. Over 40 percent of all cases of HCC occur in the People's Republic of China, which has an annual incidence of 137,000 cases. Japan has one of the highest incidence rates of HCC. The incidence appears to be decreasing in recent years. Intermediate incidence areas include several countries in Eastern and Western Europe, Thailand, Indonesia, Jamaica,

Haiti, New Zealand (Maoris), and Alaska (Eskimos). North and South America, most of Europe, Australia and parts of the Middle East are low incidence areas with fewer than three cases reported per 100,000 population per year. However, the incidence in the United States has increased during the past two decades ***(Schwartz and Carithers, 2011)***.

Risk Factors

It is unlikely that HCC is due to a single causative agent. More likely, as with other carcinomas, this tumor is the result of a complex interaction between multiple etiological factors and through a multistep mechanism.

Gender

For almost all countries, males have higher rates of HCC incidence than females, usually with a ratio of 2:1. Higher discrepancies are seen in some European states, for example, Switzerland (male:female: 4:1) and Italy (male:female: 5:1). In the developing world, the rates are more equal (China [3:1], Gambia [2.8:1] and Zimbabwe [2.4:1]). The reasons for this discrepancy are likely to be multifactorial, in part owing to higher rates of HBV and HCV infection in the male population, but also social factors, such as higher alcohol intake and obesity in men. However, testosterone levels have been shown to correlate with HCC risk, so there is probably also an innate risk