



Structure and Pathogenesis of Hepatitis C Virus in Liver Cirrhosis & Hepatocellular Carcinoma: A Narrative Review

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Abstract

Clinical outcomes of chronic hepatitis C virus (HCV) infection include liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Acute infection is usually asymptomatic, and chronic hepatitis is common. Hepatic involvement is crucial leading to liver cirrhosis and carcinoma. Pathogenesis of HCC is not yet completely understood. We tried here to discuss the structure of HCV, immune-pathogenesis, development of cirrhosis and carcinoma in diminutive and unpretentious arrangement.

Keywords: Hepatitis C Virus; Pathogenesis of HCV; Hepatic Cirrhosis; Hepatocellular Carcinoma

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Introduction

Hepatitis C virus (HCV) infection is a health problem which noticed globally. The World Health Organization (WHO) guesses that at least 170 million people (3.0% of the world's population) are infected with HCV worldwide, most of them are concerted in developing countries¹. Chronicity of the disease primes to cirrhosis, hepatocellular carcinoma and end-stage liver disease². Chronicity is obvious for 85.0% of HCV infected patients, among them 65.0% develop liver cirrhosis³. Almost 20 years after obtaining infection, 6-8% of patients with chronic Hepatitis C develop hepatocellular carcinoma⁴. Hepatic carcinoma results from HCV infection as the second cause worldwide and the liver transplantation is mainly indicated for this⁵. About 95.0% of cirrhotic liver develop HCC in chronic hepatitis C, but in case of hepatitis B, it is 60.0%⁶. Even though the particular mechanism of HCV related hepato-carcinogenesis is still not completely understood, the risk of HCC increases with the relentlessness of hepatic inflammation. Though the nature of acute illness generally asymptomatic,

persistent infection and chronic hepatitis are the hallmarks of HCV infection. HCV effectively infects hepatocytes for the induction of liver inflammation and advanced tissue damage which leads to fibrosis and cirrhosis. These are the probable cause of liver dysfunction and are assumed to initiate the commencement of liver cancer⁷. Primarily there is hepatocyte damage and necrosis followed by hepatocyte proliferation and liver regeneration. Continuous regenerative and destructive cycles substitute a condition termed as chronic liver disease that concludes in liver cirrhosis. Cirrhosis is characterized by macro regenerative nodules that, due to increased proliferative activity, are surrounded by collagen deposition and scarring. In the next progression stage, hyper-plastic nodules are observed, followed by dysplastic nodules and ultimately HCC⁸.

Epidemiology

Chronically infected persons with hepatitis C virus are estimated at 170 million, or 3% of the global population. Person's age, gender, race, and viral immune response affect the rate of chronic HCV infection. Roughly 75.0% to 85.0% of HCV-infected persons have chance to develop chronic HCV infection and are at risk for the progress to extra-hepatic manifestations, compensated and decompensated cirrhosis and hepatocellular carcinoma (HCC). It is estimated that, 10.0% to 15.0% of HCV-infected persons will progress to cirrhosis within the first 20

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years. Persons with cirrhosis are at increased risk of developing HCC⁹. The reported prevalence rates for HCV infection are lowest in the United Kingdom and Scandinavia (0.01 to 0.1%); marginally higher in the Americas, Western Europe, Australia, and South Africa (0.2% to 0.5%); and intermediate in Brazil, Eastern Europe, the Mediterranean, the Mideast, and the Indian subcontinent (1.0% to 5.0%). Egypt remains an outlier, reporting prevalence rates ranging from 17.0% to 26%¹⁰. HCV infection is variedly distributed throughout the world. Of the six genotypes, three (genotype 1, 2, and 3) are prevalent throughout the world, and the remaining 3 being restricted to particular geographical areas¹¹. HCV cases other than genotype 1 still comprise over half of all HCV cases, though genotype 1 is most frequent worldwide. Genotype 3 is mostly found in South Asia, genotype 4 in Middle East, Egypt and Central Africa and genotype 5 in South Africa. Prevalence of hepatitis C in Bangladesh is 0.8% cases¹². In case of genotype distribution, 3b is most-frequently prevalent followed by 1b¹¹. Exposure to infected blood is the primary route of transmission for HCV. Risks for transmission include blood transfusion, intravenous drug use, high-risk sexual activity, solid organ transplantation from an infected donor, occupational exposure, hemodialysis, household exposure, birth to an infected mother¹³. There is no evidence about breastfeeding is a risk factor. The risk factors of HCV transmission in hemodialysis include blood transfusions, the duration of hemodialysis, and prevalence of HCV infection in the dialysis unit, and the type of dialysis. Contaminated medical equipment, traditional medicine rites, tattooing, and body piercing are considered rare transmission routes¹⁴. Cirrhosis is the 14th most common cause of death in adults and results in 1.03 million deaths per year worldwide¹⁵. In developing countries viral hepatitis is the leading cause of cirrhosis and in the developed countries ALD, HCV and NASH are the most significant causes of cirrhosis¹⁶. The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic so the disorder is undiagnosed¹⁷.

HCC is the fifth most common cancer in the world, with more than 6 million new cases yearly¹⁸. Most cases of HCC (approximately 80%) are associated with chronic HBV or HCV infections. Areas of sub-Saharan, Western & Eastern Africa and Eastern Asia including China show the high incidence rate. Southern European countries have mid-incidence

levels whereas North America, South America, Northern Europe and Oceania have a low incidence of HCC¹⁹.

Structure of HCV

Hepatitis C virus (HCV) is a hepatotropic RNA virus of the genus Hepacivirus in the Flaviviridae family, initially replicated in 1989 as the causative agent of non-A, non-B hepatitis²⁰. The HCV genome consisting of a positive polarity 9.6-kb single-stranded RNA and an open reading frame which is single having 9033-9099 nucleotides lined by a conserved 5' and 3' non-coding region (NCR) at the ends. Its genome codes for a long poly-protein of approximately 3000 amino acids²¹ which is processed to yield three structural proteins and seven non-structural proteins²². The structural genes code for the capsid (core) protein (C) and envelope glycoproteins (E1, E2)²³. The small ion channel protein NS1/p7 is downstream of the envelope region and is required for viral assembly and release^{20,22}. The non-structural genes code for a protease (NS2) and its cofactor (NS4A), a helicase (NS3), a protein of unknown function (NS4B), a phosphoprotein (NS5A), and an RNA dependent RNA polymerase (NS5B)²⁴.

Acute HCV Infection

HCV infection is occasionally diagnosed during the acute phase because mainstream of persons have either no symptoms or only mild symptoms. The asymptomatic infection becomes chronic in most cases, and people are unaware of the infections until the end-stage liver diseases²⁵. The mean incubation period of hepatitis C ranges from 2-12 weeks. Anti-HCV and HCV RNA are found in acute phase. HCV RNA becomes positive in 2 weeks of contact. Most patients are anti-HCV positive within 8-10 weeks of exposure. Symptoms during the acute phase are non-specific and may include fatigue, lethargy, anorexia and right hypochondrial discomfort. Perhaps 25% of cases are icteric, patients with jaundice are more likely to clear the virus. Fulminant hepatitis is rare following hepatitis C infection, but has been reported, particularly following chemotherapy or withdrawal of chemotherapy. Serum ALT levels may fluctuate during the early clinical phase, and might become normal or near normal; HCV RNA may be irregularly negative during the acute phase, making the determination of true convalescence somewhat difficult. Chronic hepatitis C infection is the major complication of acute hepatitis C²⁶.

Chronic HCV Infection

The acute phase and advancement to chronic hepatitis C is usually silent. Chronic hepatitis C is arbitrarily defined as the persistence of HCV RNA in serum for 6 months or longer²⁶. In only 15%-25% of patients, HCV is self-limiting in whom HCV RNA in the serum becomes undetectable and their ALT levels return to normal. Approximately 75%-85% of infected patients can not clear the virus by 6 months, and chronic hepatitis develops⁹. Chronic disease is generally slowly progressive; cirrhosis develops within 20 years in about 10-20% of patients with chronic disease, but can remain indolent for a prolonged period of time. Anti-HCV persists for years in chronic hepatitis C. HCV RNA is usually detectable in anti-HCV positive patients and those with abnormal serum aminotransferases²⁶. Many factors such as the age at time of infection, gender, ethnicity, and the development of jaundice during the acute infection affect the rate of chronic HCV infection⁹.

Immuno-Pathogenesis of Hepatitis C Virus

Macrophages and dendritic cells present viral proteins to B cells which produce antibodies that can clear circulating virus and protect from re infection. On the cell surface, helper T cells recognize viral peptides that are phagocytosed and proteolytically cleaved HCV proteins and are presented in the environment of class II MHC molecules. On activation of their specific T-Cell receptors, HCV specific helper T-Cells assist with activation and differentiation of B-cells as well as induction and stimulation of virus-specific cytotoxic T-cells. The environment of class I MHC molecules, CD8-positive cytotoxic T-cells recognize HCV peptides that are synthesized and processed in infected cells. Some HCV proteins, such as core, E2 and NS5A affect with the immune response. The liver has been proposed as the major site where activated T-Cells are destroyed². The cellular immune reaction is a double-edged weapon. An immune response that is ineffective in clearing HCV infection may be more harmful to the liver, causing chronic inflammation, hepatocellular injury and over several decades, liver fibrosis and cirrhosis²⁷.

Development of Chronicity

The tendency to cause persistent infection is the most important feature of HCV infection. Chronically infected patients are the source of almost all new infections and are at increased risk for the development of significant chronic liver disease,

cirrhosis, and HCC. The exact mechanisms by which HCV escapes from the immune response are not completely elucidated²⁸. One hypothesis is that, once a persistent infection is established, it is difficult for HCV-specific immune response to clear HCV from all infected hepatocytes. Theoretically, this may be either due to an inadequate initiation of the primary immune reaction during acute infection or to the incompetence to maintain the T-cell response at high levels during chronic infection of HCV²⁹. The existence and the nature of quasi-species are considered mechanisms of HCV escape from immune response. The nature of quasi-species, high replication rate and the lack of proof reading capacity of HCV polymerase, contribute to the rapid diversification of viral population³⁰. NS3 and NS4A proteins form a complex which activates the NS protease domain to cleavage the IFN- β promoter stimulator (IPS-1). After cleavage, IPS-1 can no longer signal downstream to activate interferon regulatory factor-3 (IRF-3) and nuclear factor κ B (NF κ B) and the infected cells no longer produce IFN- β or express interferon stimulated genes (ISGs)³¹. HCV clearance is associated with a vigorous HCV specific CD4+ and CD8+ T cell response in the acute phase of infection. In contrast, viral persistence is associated with a weak and dysfunctional virus specific T cell response^{32,33}. Viral proteins including HCV core, E1, and NS3 inhibit dendritic cell (DC) maturation³⁴. HCV infects DCs over the binding of HCV E2 protein and thus destroy DC function in promoting an antiviral effect³⁵. HCV proteins overpower C3/C4 complement expression³⁶ and weakens membrane attack complex (MAC)-mediated microbicidal activity by suppressing C9 expression³⁷. Regulatory CD8+ T cells may play an important role in chronic HCV infection. HCV-specific CD8+CD25+FoxP3+T cells from the blood of chronically infected patients suppress HCV-specific T cell responses via TGF- β secretion. The blockade of TGF- β markedly enhances HCV specific IFN- γ secretion by CD4+ and CD8+ T cells³⁸.

Cirrhosis

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease³⁹. Causes of cirrhosis are alcoholic liver disease, chronic viral hepatitis (B or C), non-alcoholic fatty liver disease (NAFLD), primary sclerosing cholangitis (PSC), autoimmune liver disease, primary biliary cirrhosis (PBC) etc. Among them, the most common causes are

chronic viral hepatitis, prolonged excessive alcohol consumption and NAFLD worldwide⁴⁰.

Pathogenesis of Cirrhosis

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion⁴¹. This process leads to pronounced hepatic microvascular changes, characterized by sinusoidal remodeling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intra hepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction⁴². The central pathogenic procedures in cirrhosis are hepatocyte necrosis, extracellular matrix (ECM) deposition, and vascular redeployment. The deposition of collagen (types I and III) in the space of Disse, creating fibrotic septal tracts, is accompanied by the loss of fenestrations of sinusoidal endothelial cells, impairing the function of sinusoids⁴³. Hepatic fibrosis is a reply of the healing process after injury and it is categorized by accretion of extracellular matrix ("scar") which follows chronic hepatic disease⁴⁴. The predominant mechanism of fibrosis is the proliferation of hepatic stellate cells and their activation into highly fibrogenic cells producing collagen. Proliferation of hepatic stellate cells and their activation into myofibroblasts result in an increase in the expression of platelet-derived growth factor receptor β (PDGFR- β). Simultaneously, Kupffer cells and lymphocytes release cytokines and chemokines that control the expression of genes in stellate cells that are convoluted in fibrogenesis. These include transforming growth factor β (TGF- β) and its receptors, metalloproteinases, and tissue inhibitors of metalloproteinases. Throughout the procedure of liver damage and fibrosis in the progress of cirrhosis, the surviving hepatocytes are motivated to regenerate and proliferate as spherical nodules within the restrictions of the fibrous septa. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely compromised⁴³.

Natural course and Complications of Cirrhosis

The normal course of cirrhosis is categorized by an asymptomatic phase, called compensated cirrhosis, trailed by a progressive phase marked by the advancement of complications of portal hypertension and/or liver dysfunction, designated decompensated

cirrhosis. Portal pressure may be normal or below the threshold of clinically significant portal hypertension in the compensated phase of cirrhosis. Despite this normal or low pressure, esophageal varices may still appear in this phase. Decompensation is defined by the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy or jaundice. Progression of the decompensated disease may be accelerated by the development of other complications such as bleeding, refractory ascites, hepatorenal syndrome (HRS), hepatopulmonary syndrome and spontaneous bacterial peritonitis (SBP). The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage⁴⁵.

Considering the distinct prognosis of patients with compensated and decompensated liver cirrhosis, a four-stage clinical classification was proposed⁴⁶ and subsequently modified into a five-stage (2 stages in compensated and 3 stages in decompensated cirrhosis) system⁴⁷. Stage 1, fully compensated cirrhosis, no varices, no ascites; stage 2, compensated cirrhosis, presence of esophageal varices but no ascites; stage 3, bleeding of the GI tract, related to portal hypertension (esophageal varices), without another decompensating event; stage 4, ascites, jaundice or encephalopathy and stage 5, more than one complication, usually refractory ascites, intermittent encephalopathy, acute kidney injury, advanced liver dysfunction⁴⁸. The ultimate mechanism of deaths in most cirrhotic patients is progressive liver failure, complications related to portal hypertension, or the development of hepatocellular carcinoma⁴³.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) which the most common type of liver cancer in adults, classically develops in people with chronic liver disease caused by hepatitis virus infection or cirrhosis. In chronic HCV infection, the risk of HCC is associated with fibrosis stage. In cirrhotic subjects, the annual incidence of HCC is extremely high (1-7% per year), although HCC rarely develops in livers with less fibrosis^{49,50}. Although the emergence of highly effective direct-acting antivirals (DAAs) for HCV is expected to reduce the incidence of HCV-related HCC (Chung 2014), risk of HCC cannot be eliminated by the achievement of a sustained virological response (SVR), especially when the patients have already developed advanced liver fibrosis^{52,53}.

Pathogenesis of HCC

A multi-step process that may evolve over 20-40 years is HCV-induced HCC development and includes a number of steps: establishing chronic HCV infection, chronic hepatic inflammation, progressive liver fibrosis, instigation of neoplastic clones conveyed by irreversible somatic genetic/epigenetic alterations, and development of the malignant clones in a carcinogenic tissue microenvironment⁵⁴. HCV is a RNA virus with inadequate integration of its genetic material into the host's genome. Hence, the carcinogenic potential of HCV is mostly expected to be related to secondary mechanisms, even though the lack of a convenient in vitro model system to study biology is a foremost obstacle for the understanding of the mechanisms relating HCV infection, inflammation and carcinogenesis^{55,56}. Even if molecular mechanisms of HCV-induced HCC expansion have not been fully explained, these epidemiological interpretations suggest that the main role of HCV in carcinogenesis is to produce a cirrhotic tissue microenvironment that aids as a carcinogenic ambiance. Furthermore, a variety of experimental models suggested a direct carcinogenic effects of HCV proteins as supplementary drivers of HCV-induced HCC development⁵⁷. The accommodating microenvironment in cirrhosis that promotes tumor growth is commonly referred to as the cancer field effect. The cirrhotic environment that allows commencement and advancement of neoplastic clones by simplifying genetic abnormalities and cellular transformation is called the field effect or field cancerization⁵⁸. HCV infection which causes chronic damage to hepatocytes, leading to a release of inflammatory and fibrotic mediators such as reactive oxygen species, cell death signals, hedgehog ligands and nucleotides⁵⁹. Stellate cell activation is mediated by a compound series of mechanisms involving the hepatic stellate cell, mediated through intracellular inflammasome activation, the nuclear receptor family, (farsenoid-X-receptor, peroxisome proliferator-activated receptors and others) and other transcriptional events. The hepatic stellate cell which is now stimulated, promotes liver scarring through propagation, contractility, fibrogenesis, matrix degradation and inflammatory signaling. Hepatocytes, monocytes, lymphocytes and other secretory cells are infected by HCV, and contributes to stellate cell activation. HCV core and nonstructural proteins excite profibrogenic mediators such as TGF-beta⁶⁰. HCV infection induces TGFBI through reactive oxygen

species (ROS) production, p38 MAPK, JNK, ERK, and NF-kappaB pathways⁶¹. Platelet-derived growth factor (PDGF) is the supreme mitogenic signal, inducing appearance of beta PDGF receptor expression in stellate cells in common with other cell surface receptors of growth signaling for instance integrins⁶². Transgenic mice expressing PDGF-C develop liver fibrosis and HCC⁶³ and an acyclic retinoid, peretinoin, represses fibrosis and HCC development in the model⁶⁴. Relentlessness of liver fibrosis is strongly correlated with increasing risk of HCC in patients with chronic HCV infection, signifying that cirrhosis-driven carcinogenesis is the chief contrivance in the development of HCV-related HCC⁶⁵.

Natural course and complications of HCC

HCC is one of the utmost recurrent cancer types globally. Usually (up to 80% of cases) this tumor occurs in individuals who have preceding chronic liver disease and cirrhosis. The disease affects the whole body causing multiple complications of hepatocellular carcinoma including life-threatening. The pathophysiology of HCC is a composite multistep course. The interface of a number of factors is at the root of the principal steps of hepatocyte malignant transfiguration and HCC development. These aspects include a genetic predisposition, reciprocal communications between viral and non-viral risk factors, the cellular microenvironment and various immune cells, and the sternness of the underlying chronic liver disease. A reformed microenvironment is a key empowering characteristic of cancer and is known to contribute in all stages of malignant evolution, from the early transformation phases, through to invasion and, ultimately, to metastasis⁶⁶. Hepatic encephalopathy, portal vein thrombosis, worsening ascites, variceal bleeding, obstructive jaundice, and pyogenic liver abscess are the hepatic complications of hepatocellular carcinoma. A life-threatening complication of HCC is intraperitoneal bleeding.

Conclusion

In conclusion, even though a better understanding of direct and indirect mechanisms leading to HCV-induced HCC and despite the development of highly potent HCV therapy, HCV-related HCC will remain a chief health challenge in the upcoming decades. Even though prevention of HCV-induced HCC is not yet well-known, direct and indirect oncogenic roles of HCV and candidate target genes

and molecular pathways have been recommended in experimental and clinical studies. Well authenticated clinical and molecular biomarkers will be key to target subjects at the higher end of the risk spectrum with more demanding interventions, surveillance and possibly chemoprevention trials.

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None.

Conflict of Interest

There is no conflict of interest.

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Authors' contributions

Nazia Hasan Khan conceived and designed the study and wrote up the draft manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Not applicable

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