



HEPATOCELLULAR CARCINOMA AND NON-ALCOHOLIC FATTY LIVER DISEASE: A DANGEROUS LIAISON

R. NEVOLA, C. ACIERNO, F.C. SASSO, A. MARRONE, F. BUFFARDI, L.E. ADINOLFI, L. RINALDI

Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy

Abstract. Liver cancer is one of the most frequent malignancies in the world, and its incidence rates are on the rise. Due to the global epidemic of metabolic syndrome, the incidence of hepatocellular carcinoma (HCC) secondary to non-alcoholic fatty liver disease (NAFLD) is increasing, contrary to viral forms. Characteristically NAFLD-related HCCs tend to occur at the earlier stages of liver disease, while often the diagnosis of neoplasia occurs later. They also affect an averagely older population, generally with a significantly higher number of co-morbidities. For these reasons, curative treatments are seldom applicable. Therefore, this work aims to illustrate the current state of knowledge on the NAFLD-related HCC and to underline the known pathogenetic mechanisms.

KEYWORDS: Hepatocellular carcinoma, Non-alcoholic fatty liver disease, Metabolic syndrome, Insulin resistance, Inflammatory cytokines.

INTRODUCTION

Liver cancer is the sixth most common cancer all over the world. Hepatocellular carcinoma (HCC) is the most common histological type, accounting for 90% of the cases of liver cancer^{1,2}. HCC is the fourth leading cause of cancer-related deaths worldwide, with about 810.000 deaths per year^{3,4}; in addition, while the number of diagnosis of other neoplasms is decreasing, the rate of incidence of liver cancer appears to be increasing⁵.

Despite the revolution in antiviral treatments and epidemiology, at present, the main causes of HCC are viral infections (such as hepatitis B virus – HBV, and hepatitis C virus – HCV) and alcohol abuse. However, the current epidemic of obesity and metabolic syndrome, which is affecting the Western countries, is leading to a significant increase in HCC secondary to non-alcoholic fatty liver disease (NAFLD)^{4,6}. In fact, an annual increase of 9% in the incidence rates

of NAFLD-associated HCC is occurring. Looking forward to the future, this condition may become the main factor of HCC, leading to a significant switch between metabolic and viral forms⁷. HCC typically occurs in a setting of cirrhosis, but approximately 20% of HCCs have been observed to develop in a non-cirrhotic liver^{8,9}. This sub-group of HCC often appears at advanced stages, possibly because the lack of adequate monitoring in a non-cirrhotic liver, especially in the context of metabolic disease. There are poor data on HCCs in non-cirrhotic liver; since HCC is one of the fastest growing causes of cancer-related deaths and accounts for a survival rate of less than 12%, there is an impending need for further research to explore the epidemiology of non-cirrhotic HCC¹⁰. This review of the literature aims to provide an update on the current state of knowledge in the field of liver cancer secondary to NAFLD, in order to improve prevention, diagnosis and treatment of this growing problem.



NON-ALCOHOLIC FATTY LIVER DISEASE

Due to the current epidemic of obesity and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) is the world's fastest growing chronic liver disease. It is estimated that in the general population the global prevalence of NAFLD is currently at 25%. It is characterized by the intrahepatic accumulation of triglycerides and encompasses a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), to cirrhosis (defined metabolic or cryptogenic cirrhosis), with a significant capability of progressing from one form into another. In particular, the presence of necro-inflammatory hepatic activity separates a picture of simple steatosis from one of NASH, which typically presents a histological picture associated with signs of chronic inflammation, whether or not fibrosis occurs. The chronic damage sustained by NASH can indeed progressively lead to the development of liver fibrosis and its evolution towards frameworks of overt cirrhosis and its complications, including liver failure and hepatocellular carcinoma (HCC)¹¹. In this regard, the annual incidence of HCC in patients with NAFLD is equal to 0.44 cases per 1000 patients, while the annual incidence in patients who have already developed NASH is equal to 5.29 cases per 1000 patients. It is estimated that in the United States NAFLD is responsible for about 14% of HCCs, with an annual growth rate of 9%¹².

As mentioned, NAFLD is now the chronic liver disease with the highest rates of increase worldwide, with an estimated prevalence of about 25% in the adult population. The prevalence of NASH is instead around 3-5%. Females appear to be more affected by both diseases. The prevalence of NAFLD also appears to be extremely variable on a global level. In Europe, it is around 24% with peaks in Greece and Spain (up to 40%). Degree and prevalence of liver fibrosis secondary to NAFLD also tend to increase progressively with age, due to a longer duration of the disease as well as longer exposure to factors of hepatic injury¹³. Its prevalence appears to increase with a direct proportion with the increase in the body mass index (BMI). In this context, the prevalence of NAFLD in the general population hits over 90% in the severely obese who need weight reduction through bariatric surgery. In fact, there is a close correlation between metabolic syndrome and NAFLD, the latter being the organ manifestation in the liver. A high-calorie diet, high in fat and refined carbohydrates, as well as a sedentary lifestyle, are factors associated with increased weight and consequently the onset of NAFLD¹².

Despite its close association with obesity and metabolic syndrome, a non-negligible proportion of patients with NAFLD (about 7%) appears

to be free from these characteristics. When present in non-obese individuals, NAFLD seems to be related to the presence of unfavorable genetic polymorphisms at the level of the genes involved in the regulation of triglyceride mobilization from lipid droplets (PNPLA3), in the secretion of VLDL (TM6SF2) or in the remodeling of the acyl chain of hepatic phosphatidyl-inositol (MBOAT7). Despite the "lean" phenotype, these patients develop insulin resistance and pro-atherogenic lipid alterations similar to those of obese patients, with whom they share the cardio-metabolic risk and the hepatic damage¹².

PATHOGENESIS OF NAFLD-RELATED HCC

Regardless of etiology, any form of chronic damage to the liver, results in a state of low-grade inflammation. The latter is able to feed the progression of liver fibrosis and promote the induction of cell proliferation. In fact, the high cellular turnover to which chronic damage exposes determines a high rate of genetic errors, whose accumulation creates the prerequisite for hepatocarcinogenesis¹⁴. For this reason, liver cirrhosis is itself a premalignant condition and a risk factor for HCC, regardless of etiology of the damage.

However, increasing evidence suggests that NAFLD may cause the development of HCC even in non-cirrhotic patients with mild or absent fibrosis¹⁵⁻²¹. At present, there are conflicting data on the actual prevalence of HCC in non-cirrhotic steatotic liver²². Recently, extensive literature reviews show an extremely low risk of developing HCC on NAFLD in the absence of liver cirrhosis¹⁹. On the other hand, several studies highlight a non-negligible incidence rate of HCC in this setting^{16,17,20,21,23}. In animal models, it appears that steatosis, before cirrhosis, is a pre-malignant condition²⁴. Therefore, the assessment of possible damage cofactors is essential to individualize the risk of HCC. In particular, obesity and diabetes mellitus are independent hepatocarcinogenic factors and can act synergistically in raising the risk of cancer²⁵⁻²⁹. The risk appears to be further increased in the presence of additional damage cofactors, potentially represented by chronic alcohol consumption or chronic HCV or HBV infection^{30,31}. In the pathogenesis of NAFLD-related HCC, several factors act synergistically, thus favoring the proliferation of the neoplastic clone, according to what is defined "multiple hits hypothesis"^{13,32-39}. A key role in the process of hepatocarcinogenesis in NAFLD is played by insulin resistance (IR). It is in fact able to promote the release of fatty acids free from adipose tissue and their accumulation in the liver¹⁰.

As previously mentioned, the accumulation of intrahepatic triglycerides, in fact, causes a state of chronic low-grade inflammation, independently of the presence of significant liver fibrosis. This causes oxidative stress, lipid peroxidation, mitochondrial damage and endoplasmic reticulum dysfunction. Insulin resistance itself is a stimulus to the production of pro-inflammatory cytokines (ex: TNF- α) with subsequent activation of the nuclear factor Kappa B (NF- κ B) and of the N-terminal kinase c-Jun (JNK) on one side, as well as to the overexpression of tumor growth promotion genes on the other side^{34,35}. JNK appears to be overexpressed in more than half of the cases of HCC and causes, in turn, the phosphorylation of substrate-1 of the insulin receptor (IRS-1). The signaling mediated by IRS1 can, therefore act as a stimulus for cell survival, promoting the proliferation of hepatocytes through the mitogen-activated protein kinase and PI3K, and inhibiting cell apoptosis by blocking the TGF- β ³⁶. The cytokinetic imbalance associated with the release of unsaturated fatty acids also contributes to the inhibition of tumor suppression factors and of cell apoptosis³⁷. The oxidative stress thus generated also favors lipid peroxidation and consequent mutations of tumor suppressor genes (such as p53), favoring carcinogenesis and the progression of HCC³⁸. The overproduction of pre-inflammatory cytokines also stimulates the production of leptin, which acts as a growth factor^{39,40}. This step represents an important step in promoting the proliferation of neoplastic cellular clones. In fact, high levels of leptin are closely associated with a higher risk of neoplastic recurrence after a potentially curative treatment of HCC⁴⁰. At the same time, IR is able to inhibit the production of adiponectin from adipose tissue. It is a cytokine with anti-inflammatory, anti-proliferative, pro-apoptotic, anti-atherogenic and insulin-sensitizing properties. Due to such effects, the inhibition of adiponectin production correlates with an increased carcinogenic risk^{22,41}. Metabolic imbalance also promotes the migration of immune cells to the liver, which can activate the signal cascade feeding the pre-existing inflammatory state induced by NAFLD⁴². Alterations in the intestinal microbiota would also seem to contribute to the pathogenesis of hepatic inflammatory states⁴³. Interacting with the toll-like receptors (TLRs) on hepatic stellate cells, endotoxemia would feed the inflammatory cascade, contributing to liver injury and oncogenesis processes⁴⁴.

CLINICAL FEATURES OF NAFLD-RELATED HCC

Compared to the forms of liver cancer secondary to viral or exotoxic etiologies, NAFLD-related

HCC shows some peculiarities. In fact, it affects an averagely older population (with a high prevalence of cardiovascular disease) and manifests at an earlier stage of liver disease^{30,45,46}. With regards to laboratory data, NAFLD-related HCCs seem to show lower transaminase values and a minor prevalence of thrombocytopenia^{46,47}. If the onset of HCC occurs at an early stage of liver disease, on the other hand the stage of the neoplasia at the diagnosis often appears more advanced (larger and more frequent infiltration or multifocal lesions) than what usually occurs for other etiologies^{21,23,47}. Less attention during the follow-up of NAFLD (rather than viral etiologies) may account for the often-late diagnosis, more frequently incidental and external to the usual screening protocols¹⁹. Moreover, the frequently lower diagnostic sensitivity for early small-sized tumors of the ultrasound method in obese patients cannot be neglected^{48,49}. An advanced stage of cancer at diagnosis leads to a lower number of radical therapy that can be used in these patients compared to other etiologies. In fact, palliative methods are often used (e.g. chemoembolization or systemic therapies). In addition, patients with metabolic syndrome who develop HCC suffer from numerous co-morbidities and are averagely older, as previously mentioned. This results in a low rate of liver transplants and in general a worse prognosis than patients with HCC secondary to other etiologies^{12,21,23,45}. In fact, the rate of death within the first year after a diagnosis of HCC is 61% for patients with NAFLD and 50% for forms with viral etiology, with a 5 months lower life expectancy^{12,21}. To confirm the fact that the worst prognosis derives exclusively from a late diagnosis, when curative treatments such as resection or ablation can be applied, survival rates are absolutely overlapping among the various etiologies⁴⁸.

CONCLUSIONS

NAFLD-related HCC shows an increase in the incidence rates. The rapid decline of viral forms, due to effective therapies (HBV and HCV) and vaccines (HBV), the epidemic of obesity and metabolic syndrome, will make NAFLD-related HCC the most common form of liver cancer. The widespread of the knowledge about the topic is, therefore, necessary, as well as dedicated screening and follow-up paths, in order to reduce the incidence and anticipate the diagnosis.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interests



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