Non-Alcoholic steatohepatitis and primary hepatic carcinoma

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SUMMARY
Non-alcoholic fatty liver disease (NAFLD) has been recognized as the most frequent cause of chronic liver disease and comprises a spectrum of chronic liver diseases ranging from simple hepatic steatosis, to hepatic steatosis with non-specific hepatic inflammation, to non-alcoholic steatohepatitis (NASH) and finally cirrhosis. The prevalence of NAFL and NASH in the general population of the United States is estimated at 20% and 3% respectively and can be as high as 95% in high-risk subgroups with abnormal liver enzymes, type 2 diabetes mellitus, or morbid obesity. Prevalence of NASH has been reported in more than 50% in obese individuals with body mass index >30 and in patients with diabetes mellitus type II, but its prevalence in lean individuals can be as high as 35%. NAFLD has been implicated in the pathogenesis of cryptogenic cirrhosis as a major cause; in fact 30-40% of cases of cryptogenic cirrhosis have been attributed to NAFLD, while 15-30% of patients with cryptogenic cirrhosis manifest histological findings compatible with NASH.

INTRODUCTION – EPIDEMIOLOGY
Non-alcoholic fatty liver disease (NAFLD) has been recognized as the most frequent cause of chronic liver disease and comprises a spectrum of chronic liver diseases ranging from simple hepatic steatosis, to hepatic steatosis with non-specific hepatic inflammation, to non-alcoholic steatohepatitis (NASH) and finally cirrhosis. The prevalence of NAFL and NASH in the general population of the United States is estimated at 20% and 3% respectively and can be as high as 95% in high-risk subgroups with abnormal liver enzymes, type 2 diabetes mellitus, or morbid obesity. Prevalence of NASH has been reported in more than 50% in obese individuals with body mass index >30 and in patients with diabetes mellitus type II, but its prevalence in lean individuals can be as high as 35%. NAFLD has been implicated in the pathogenesis of cryptogenic cirrhosis as a major cause; in fact 30-40% of cases of cryptogenic cirrhosis have been attributed to NAFLD, while 15-30% of patients with cryptogenic cirrhosis manifest histological findings compatible with NASH.

NATURAL HISTORY AND CHARACTERISTICS OF NON-ALCOHOLIC FATTY LIVER DISEASE
The diagnosis of NAFLD is suspected in patients with elevated liver enzymes who do not consume significant amounts of alcohol (less than 210 g of alcohol in men and less than 120 g of alcohol in women per week, or even more rigorously less than 70 g of alcohol per week) and are obese, or have diabetes mellitus type 2 or hypertriglyceridemia and in general have insulin-resistance and features of the metabolic syndrome. Other causes of chronic liver disease should be excluded, mainly viral, autoimmune hepatitis and hepatotoxic medications. Ultrasound examination is quite sensitive in the detection of NAFLD and the liver appears hyperechoic in most cases. Despite that, the specificity of ultrasound findings is less than 90% and the diagnosis is confirmed only by pathological evaluation of an adequate liver specimen, at least 2 cm long, which also has prognostic value. Liver histology of NAFLD is classified into 4 subtypes; type I is characterized by fatty degeneration, type II by fatty degeneration and lobular non-specific inflammation, type III by all the above and ballooning degeneration of hepatic...
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tocytes and type IV by all the above and fibrosis. Types
III and IV characterize NASH and can progress to cirrho-
sis.

Five and ten year survival rates in patients with NASH
is 67% and 59% respectively, but death is usually caused
by cardiovascular complications of diabetes mellitus, obes-
ity and hyperlipidemia. The rate of development of
cirrhosis by NASH has been reported to be higher than
that by chronic hepatitis C (20% versus 15% in 20 years). In
a recent study, 25% of patients with NASH progressed
to cirrhosis and 11% died of liver-related causes.3

FACTORS ASSOCIATED WITH
NON-ALCOHOLIC FATTY LIVER DISEASE
AND HEPATOCELLULAR CARCINOMA

Angulo et al have proposed simple markers for the
prediction of worsening liver histology in NASH. Inde-
pendent predictors of liver fibrosis in patients with non-
alcoholic steatohepatitis were age >40 years old, in-
creased BMI index, presence of type II diabetes melli-
tus, hypertriglyceridemia, ALT >100 IU/L (normal val-
ues <40), AST/ALT ratio >1 and increased levels of IgA
immunoglobulins in serum.1,6

In general, most cases of hepatocellular carcinoma
are diagnosed in patients ho have had cirrhosis for many
years. However it is not clear whether the neoplastic pro-
cess begins during cirrhosis or starts at earlier stages of
liver disease. If hepatocellular carcinoma begins during
cirrhosis, then it is reasonable to speculate that hepatic
insulin resistance might be involved, because advanced
liver disease is generally associated with insulin resistance
and the association between cirrhosis and diabetes is
particularly strong in obese individuals.7

An experimental controlled study in genetically
obese, leptin-deficient ob/ob mice, which are models of
NAFLD, found, by comparing parameters of prolifera-
tion and apoptosis, that hepatic hyperplasia was evident
at the earliest stage of NAFLD in ob/ob mice, which sup-
ports the concept that obesity-related metabolic abnor-
malities, rather than cirrhosis, initiate the hepatic neo-
plastic process during obesity.8

In cryptogenic cirrhosis, an overall prevalence of 6.9%
of hepatocellular carcinoma was founds, lower than the
prevalence of hepatocellular carcinoma arising in cirrho-
sis related to alcohol or viral hepatitis, but higher than
that for hepatocellular carcinoma arising in cirrhosis re-
lated to primary biliary cirrhosis. An univariate analysis
showed that patients with cryptogenic cirrhosis and hepa-
tocellular carcinoma were more likely to have type 2 dia-
betes mellitus, hypercholesterolemia, hypertrigly-

ceridemia and to have correspondingly higher fasting
levels of glucose, cholesterol and triglycerides. Insulin
resistance was also significantly associated with hepato-
cellular carcinoma arising in patients with cryptogenic
cirrhosis. Current BMI was similar between cases and
controls but “precirrhosis BMI” was significantly higher
in the cases. Curiously, serum aminotransferases were
significantly lower in cases compared with controls. A
multivariate analysis showed that hypertriglyceridemia,
type 2 diabetes and normal alanine aminotransferase
were independently associated with cryptogenic cirrho-
sis and hepatocellular carcinoma. The importance of
these findings remains to be defined, but one could spec-
ulate that hepatocellular carcinoma is part of the clinical
spectrum of NAFLD and the metabolic derangement
observed in patients with NAFLD may underlie the pro-
gression of liver disease to cirrhosis and hepatocellular
carcinoma.

REPORTS OF HEPATOCELLULAR
CARCINOMA IN PATIENTS WITH
NON-ALCOHOLIC-FATTY LIVER DISEASE

Few reports have been published so far about the in-
cidence of primary hepatic carcinoma in patients with
NAFLD and NASH. In 1998, a British group excluded
hepatitis G virus as a risk factor for hepatocellular carci-
noma, but also noticed that patients with cryptogenic cir-
rhosis who had developed hepatocellular carcinoma had
histological features of NASH.4

In 2001, a Japanese group reported a case of NASH
with multicentric hepatocellular carcinoma in a female
patient.9 At the age of 58 years, the patient was diag-
ized with non-insulin-dependent diabetes mellitus,
treated by insulin therapy. She was negative for all sero-
logical markers of hepatitis B and C virus infection and
denied consuming alcohol. Because of liver dysfunction,
a needle biopsy was performed at the age of 62 years
and pathological findings, such as fatty change, Mallory’s
body, nuclear glycogen and pericellular fibrosis, sugge-
sted a diagnosis of NASH. Subsequently, four nodules
were detected in the liver by imaging, and needle biopsy
of the nodules confirmed the diagnosis of hepatocellu-
lar carcinoma. Cancer was diagnosed 10 years after the
diagnosis of NASH. The authors suggested that hepato-
cellular carcinoma could be a late complication of NASH.

Shimada et al reported six patients with hepato-
cellular carcinoma in a group of 82 patients with NASH,10
three of whom were referred with hepatocellular carcinoma. In five of these six patients, NASH was associated with obesity, hyperlipidemia or diabetes mellitus. The carcinomas measured 1.5-6.0 cm in size and were well differentiated in three of the six cases. Since fibrosis and cirrhosis were present in all patients with NASH complicated by hepatocellular carcinoma, patients at risk probably could be identified by the same histological and clinical markers that herald disease progression in uncomplicated NASH.

In another single American centre study, one hundred and five consecutive patients with hepatocellular carcinoma were studied. The most common etiology of underlying liver disease was hepatitis C (51%) and cryptogenic cirrhosis (29%). Half of the patients with cryptogenic cirrhosis had histological or clinical features associated with NAFLD, so NAFLD accounted for at least 13% of the cases of hepatocellular carcinoma. Patients with cryptogenic cirrhosis were less likely to have undergone surveillance for hepatoma and had larger tumors at diagnosis. Ultrasound examination in combination with alpha-fetoprotein and des-γ-carboxyprothrombin (a newer marker) every three months appears to be a sensitive and intensive surveillance programme for the early detection of hepatocellular carcinoma.

Finally, in an Italian retrospective study, among 641 patients with cirrhosis associated hepatocellular carcinomas, 44 patients with cryptogenic cirrhosis were identified. Of these, 23 were actively followed up and were compared in a case-control study with viral and alcohol associated hepatocellular carcinoma. Although liver function was similar, cryptogenic cirrhosis patients had higher glucose, cholesterol and triglyceride plasma levels, increased parameters of insulin resistance, and lower aminotransferase levels. Logistic regression analysis identified in sequence hypertriglyceridemia, diabetes and normal aminotransferases as independent factors associated with hepatocellular carcinoma arising in cryptogenic cirrhosis. Thus, features suggestive of NASH were more frequently observed in hepatocellular carcinoma arising in patients with cryptogenic cirrhosis than in age and sex matched hepatocellular carcinoma patients of well-defined viral or alcoholic etiology. The authors conclude that hepatocellular carcinoma may represent a late complication of NASH-related cirrhosis.

CONCLUSIONS

NAFLD appears to be a common cause of the underlying liver disease in patients with hepatocellular carcinoma, but a prospective study of patients with NASH is necessary to confirm the etiologic association and to determine the risk of development of hepatocellular carcinoma in this population. NAFLD may be an important cause of cryptogenic cirrhosis as well as hepatocellular carcinoma.

In conclusion, the whole spectrum of liver disease may stem from a metabolic derangement and attempts should be made to interrupt the progression from simple fatty liver disease to steatohepatitis, fibrosis, cirrhosis and ultimately hepatocellular carcinoma. A behavioural approach, such as diet and exercise, to reduce the prevalence and the progression of obesity, diabetes and dyslipidemia, as well as the pharmacologic treatment of insulin resistance and the use of newer therapeutic agents of NASH, merit consideration in this clinical setting.

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