



Nonalcoholic steatohepatitis-associated hepatocellular carcinoma: Our case series and literature review

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HCC is necessary in non-cirrhotic NASH patients as well as cirrhotic patients.

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Abstract

Recently, nonalcoholic steatohepatitis (NASH) has been considered to be another cause of liver cirrhosis and hepatocellular carcinoma (HCC). The natural history and prognosis of NASH are controversial. Accordingly, we assessed the clinicopathological features of NASH-associated HCC in our experience and reviewed the literature of NASH-associated HCC. We experienced 11 patients with NASH-associated HCC (6 male, 5 female; mean age 73.8 ± 4.9 years) who received curative treatments. Most (91%) patients had been diagnosed with obesity, diabetes, hypertension, or dyslipidemia. Seven patients (64%) also had a non-cirrhotic liver. The recurrence-free survival rates at 1, 3 and 5 years were 72%, 60%, and 60%. We also summarized and reviewed 94 cases of NASH-associated HCC which were reported in the literature (64 male; mean age 66 years). The majority of patients (68%) were obese, 66% of patients had diabetes, and 24% had dyslipidemia. Furthermore, 26% of the HCCs arose from the non-cirrhotic liver. In conclusion, patients with non-cirrhotic NASH may be a high-risk group for HCC, and regular surveillance for

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignancy in Asia and South Africa. HCC usually develops in patients with hepatitis B, hepatitis C, and alcoholic liver disease. Recently, nonalcoholic steatohepatitis (NASH) has been considered to be another cause of liver cirrhosis and HCC. Powell *et al*^[1] reported the first case of NASH-associated HCC. Since then, several case series of NASH-associated HCC have been reported^[2-4].

The prevalence of nonalcoholic fatty liver disease (NAFLD) is 10%-30% in adults^[5] and its prevalence is increasing in Japan as well as Western countries because of the epidemic rise in obesity and diabetes mellitus (DM). NASH is part of the spectrum of NAFLD, and 20% of NASH cases are thought to slowly progress to cirrhosis^[6]. According to a previous study^[7], NASH can progress to cirrhosis and result in complications including HCC.

Almost all patients with cryptogenic cirrhosis (CC) had clinical features consistent with NASH, but a diagnosis of NASH could not be confirmed by histology (likely “burnt out NASH”)^[8]. The natural history and prognosis of NASH is controversial, because there are few reports on prospective cohort studies of NASH^[9,10]. Accordingly, it is necessary to clarify an etiology and a prognosis of NASH-associated HCC. Thus, we retrospectively assessed the clinicopathological features of NASH-associated HCC in our experience and reviewed the literature on NASH-associated HCC.

NASH-ASSOCIATED HCC IN OUR EXPERIENCE

We reviewed 797 consecutive patients treated for primary HCC at National Hospital Organization Iwakuni Clinical Center from January 1996 and September 2008. Of these, 445 with HCC initially underwent curative treatment. Curative treatment was defined as complete tumor eradication, with no residual tumor visible by computed tomography (CT), or resection of all evident tumor tissue, and no tumors detected in the remnant liver on CT scan performed 3 to 4 wk after curative treatment. Curative treatment included surgery, percutaneous radiofrequency ablation (RFA), microwave coagulation therapy (MCT), and percutaneous ethanol injection (PEI). Within this group, 11 patients were considered to have NASH based on the histology of the non-cancerous parts of the surgical specimens or biopsy specimens.

NASH was diagnosed using the following criteria^[3]: (1) histological features of steatohepatitis; (2) intake of less than 20 g ethanol per day; (3) absence of other liver diseases such as autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, and metabolic liver disease such as Wilson’s disease and hemochromatosis; and (4) negative for hepatitis B surface antigen and antibody to hepatitis C virus (HCV) and/or negative for HCV RNA on polymerase chain reaction analysis.

The body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). The definition of DM was fasting plasma glucose level ≥ 126 mg/dL on at least two occasions, plasma glucose level of ≥ 200 mg/dL at 2 h in a 75 g oral glucose tolerance test, or the need for insulin or an oral antihyperglycemic drug to control glucose levels. The oral glucose tolerance test was undertaken by patients who had no medical history of DM.

Dyslipidemia was defined as blood total cholesterol concentration > 220 mg/dL or triglyceride > 150 mg/dL or a history of taking oral drugs for dyslipidemia.

The histological status of underlying liver disease was based upon microscopic examination of the non-cancerous part of the surgical specimen or biopsy specimen with hematoxylin-eosin and Azan staining. All liver tissue specimens were evaluated by two senior pathologists who were unaware of the laboratory data and the clinical course. Steatohepatitis was pathologically graded on quantified

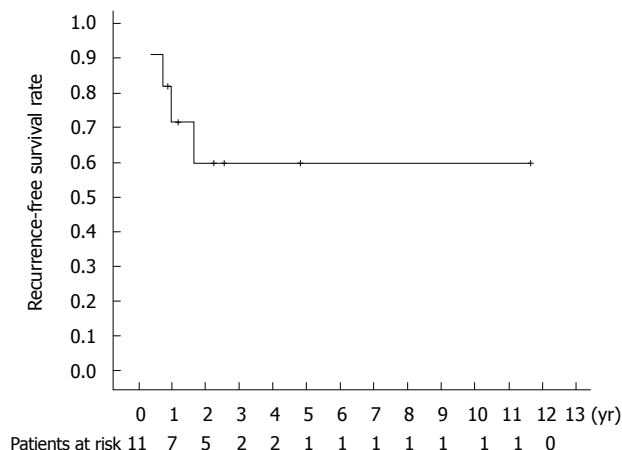


Figure 1 Recurrence-free survival rates in nonalcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC).

steatosis, ballooning degeneration, and lobular inflammation to produce an NAFLD activity score (NAS)^[11]. When this score is ≥ 5 it is diagnostic for NASH. The extent of fibrosis, established by Desmet *et al.*^[12], is as follows: F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), and F3 (severe fibrosis) were all categorized non-cirrhosis. F4 was categorized as cirrhosis.

A summary of our 11 cases with NASH-associated HCC is shown in Table 1. The mean age of patients with HCC was 73.8 ± 4.9 years. Of the 11 patients, 6 patients (55%) were male, and 5 (45%) were female. The mean BMI was $24.8 \text{ kg}/\text{m}^2$. Six patients (55%) were obese (BMI $\geq 25 \text{ kg}/\text{m}^2$), 6 (55%) had DM, 3 (27%) had dyslipidemia, and 6 (55%) had hypertension. Ten patients (91%) had obesity or at least 1 comorbid illness. The prevalence of positivity of HBV core (HBc) antibodies in our cases was 27% (3 of 11 patients). Ten patients (91%) had Child-Pugh classification A and 1 (9%) was Child-Pugh classification B, and all patients received curative treatments as outlined below. Seven patients (64%) received surgery, 3 patients (27%) received RFA, and 1 patient (9%) received MCT. Four patients (36%) had concomitant liver cirrhosis (F4), and 7 patients (64%) had a non-cirrhotic liver (F1-3). Concerning the characteristics of HCC, 8 patients (73%) had a single nodule, 3 patients (27%) had multinodular lesions, and the mean size of the largest lesion was 3.3 ± 1.3 cm (range 1.7-5.0 cm).

Patients were followed for 41.3 ± 40.0 mo (range, 9.4-151.7 mo), and no patients dropped out. Local tumor progression was not found. The recurrence-free survival rates at 1, 3, and 5 years calculated by Kaplan-Meier method were 72%, 60%, and 60% (Figure 1). All of tumor recurrences were observed within the first 2 years, and no recurrence was observed after 2 years. During the follow-up, 3 patients (27%) died as a result of HCC (2 patients) and hepatic failure (1 patient).

EPIDEMIOLOGIC TRENDS OF NASH AND NASH-ASSOCIATED HCC

HCC is the third leading cause of cancer death in world-

Table 1 Characteristics of 11 NASH patients with HCC undergoing curative treatment

Case	1	2	3	4	5	6	7	8	9	10	11
Sex (M/F)	M	F	F	M	M	M	F	F	F	F	M
Age (yr)	73	73	83	75	67	68	77	79	73	76	68
BMI	25.0	23.6	21.0	22.3	25.3	24.2	28.1	25.3	23.4	28.8	26.2
Diabetes mellitus (yes/no)	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Dyslipidemia (yes/no)	No	Yes	No	Yes	No	No	No	No	No	No	Yes
Hypertension (yes/no)	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes
Total bilirubin (mg/dL)	1.6	0.6	0.6	0.7	1.4	0.8	0.8	1.2	0.6	1.3	0.9
Albumin (g/dL)	3.9	4.4	3.2	3.8	4.4	4.3	3.5	4.1	4.4	3.8	4.9
ALT (IU/L)	73	41	22	24	73	18	19	29	41	40	57
γ GTP (IU/L)	110	45	36	22	57	33	26	111	124	41	177
Prothrombin time (%)	78.1	95.8	96.3	106.6	90.9	113.4	75.4	77.2	94.0	68.4	86.0
Platelets ($\times 10^4/\mu\text{L}$)	10.1	15.0	15.1	27.8	14.3	27.2	9.3	13.9	13.0	5.5	13.4
Child-Pugh classification (A/B)	A	A	A	A	A	A	B	A	A	A	A
AFP (ng/mL)	8.7	4.6	40.6	9181.6	1.7	1.8	1957.0	7.9	13.0	8.8	16.2
DCP (mAU/mL)	31	10	2066	1765	64	10	718	19	571	106	2930
Anti-HBc (+/-)	+	-	-	-	-	+	-	-	-	+	-
Treatment (RFA/MCT/Ope)	RFA	RFA	Ope	Ope	Ope	Ope	Ope	Ope	RFA	MCT	Ope
No. of nodules (1/2/3)	3	1	1	1	1	1	1	1	3	2	1
Size of largest tumor (cm)	1.8	1.7	5.0	5.0	3.6	4.5	3.2	2.0	2.5	3.0	4.4
Stage of fibrosis (F1/F2/F3/F4)	F4	F1	F4	F1	F1	F1	F4	F4	F1	F3	F1

NASH: Nonalcoholic steatohepatitis; HCC: Hepatocellular carcinoma; M: Male; F: Female; BMI: Body mass index; ALT: Alanine aminotransferase; γ GTP: γ -glutamyltransferase; AFP: α -fetoprotein; DCP: Des- γ -carboxy prothrombin; Anti-HBc: HBc antibody; RFA: Radio-frequency ablation; MCT: Microwave coagulation therapy; Ope: Operation.

wide; there are an estimated 500 000 to 1 million new cases each year resulting in 600 000 deaths annually^[13]. The major causes of cirrhosis seen in HCC are viral (hepatitis B, hepatitis C), and alcohol. HCV infection is the most prevalent risk factor for HCC in Japan and United States. In United States, the most leading etiology underlying liver disease among the patients with HCC was HCV (51%), and the second most common etiology was CC (29%)^[14].

In the majority of CC cases it is thought to be end-stage NASH because some clinical features such as obesity and diabetes in CC patients are linked to NASH. However, histology often is no longer informative when cirrhosis is already established^[15] because it has been theorized that CC often represents “burned out” NASH. Marrero *et al*^[16] studied the etiology of liver disease in 150 patients with HCC wherein NAFLD-related CC accounted for at least 13% of the cases.

CLINICOPATHOLOGICAL FEATURES

Articles were searched in Medline and Pubmed. The search terms used were NASH, nonalcoholic steatohepatitis, fatty liver, HCC, hepatocellular carcinoma, hepatoma, and liver neoplasms. We summarized and reviewed several studies and numerous case reports which explored NASH-associated HCC^[1-4,17-31]. At least 94 cases of NASH-associated HCC were reported (Table 2). Sixty-four patients were male (64%), and the age at diagnosis ranged from 35 to 89 years (mean, 66 years). The majority of patients (68%) were obese, 66% of patients had DM, and 24% had dyslipidemia. Concerning tumor characteristics, 69% of HCCs were multinodular, maximum tumor size ranged from 1.4-13 cm (mean, 3.5 cm). Furthermore,

26% of cases arose from a non-cirrhotic liver. In a case-controlled study of 34 Japanese NASH-associated HCC patients, those patients were predominantly male, had a median age of 70 years and 88% had advanced fibrosis. Older age, low level of AST, low grade of activity, and advanced fibrosis were independent predictors of developing HCC in NASH^[3].

NATURAL HISTORY AND PROGNOSTIC FACTORS

The natural history and prognosis of NASH is controversial because there are few reports on prospective cohort studies of NASH^[3,9,10].

Yatsuji *et al*^[10] reported that the 5-year HCC rate was 11.3% for NASH-cirrhosis and 30.5% for HCV-cirrhosis in Japanese patients. On the other hand, Hui *et al*^[9] reported that HCC occurred in 8 (17%) of 46 patients with HCV-cirrhosis compared with none of 23 patients with NASH-cirrhosis after 5 years follow-up in Australia.

A prospective cohort study of NASH patients in Japan^[3] showed that the 5-year cumulative incidence of HCC was 7.6%, and the 5-year survival rate was 82.8%. Concerning outcome, 26 of 137 NASH patients died, with death caused by liver failure in 7 patients, HCC in 12 patients and other causes in 7 patients. Liver-related deaths thus accounted for 19 (73%) deaths.

Malik *et al*^[4] reported that the survival rate after liver transplantation for HCC complicated NASH-cirrhosis was 88% at a mean follow-up of 2.5 years. There was no difference in 5-year survival between patients transplanted for NASH-cirrhosis with and without HCC, and no difference in 5-year survival after liver transplantation between

Table 2 Clinical features of cases with NASH-associated HCC in previous reports

Author	No. of cases	Age (yr)	Sex	Underlying disease	Liver histology	No. of nodules	Tumor size (cm)	Treatment
Powell <i>et al</i> ^[1]	1	57	F	DM	LC	Mul	NR	Ope
Zen <i>et al</i> ^[17]	1	72	F	DM	LC	Mul	1.4	NR
Orikasa <i>et al</i> ^[18]	1	67	F	DM	LC	Sol	2.6	NR
Cotrim <i>et al</i> ^[19]	1	66	M	OB, DM	LC	Sol	3.0	PEI
Bencheqroun <i>et al</i> ^[20]	1	68	M	OB	Non-LC	NR	NR	NR
Mori <i>et al</i> ^[21]	1	76	M	OB, DM	LC	Sol	1.9	RFA
Bullock <i>et al</i> ^[22]	2	64, 74	M (2)	OB (2), DM (2)	Non-LC (2)	Sol (2)	NR	Ope (2)
Cuadrado <i>et al</i> ^[23]	2	69, 74	M (2)	OB (2), DM (2)	LC, Non-LC	Sol (2)	NR	RFA (2)
Sato <i>et al</i> ^[24]	1	64	M	OB, DL	Non-LC	Sol	13.0	None
Ichikawa <i>et al</i> ^[25]	2	60, 66	M, F	OB (1), DL (1)	Non-LC (2)	Sol (2)	1.5, 2.5	Ope (2)
Ikeda <i>et al</i> ^[26]	1	69	M	OB, DM	LC	Sol	4.5	Ope
Tsutsumi <i>et al</i> ^[27]	2	46, 68	M, F	NR	LC (2)	Sol (2)	NR	NR
Hashizume <i>et al</i> ^[2]	9	45-82	M (5), F (4)	OB (5), DM (7), DL (8)	LC (6), Non-LC (3)	Sol (8), Mul (1)	1.5-7.0	Ope (6), RFA (2), TAE (1)
Hai <i>et al</i> ^[28]	2	65, 72	M (2)	OB (2), DM (2)	LC, Non-LC	Sol (2)	4.0, 6.0	Ope (2)
Maeda <i>et al</i> ^[29]	3	52-68	M (2), F (1)	NR	LC (3)	Sol (3)	1.3-5.0	Ope (3)
Kawada <i>et al</i> ^[30]	6	59-81	M (3), F (3)	OB (2), DM (3), DL (1)	Non-LC (6)	Sol (6)	1.3-5.8	Ope (6)
Hashimoto <i>et al</i> ^[3]	34	54-89	M (21), F (13)	OB (62%), DM (74%), DL (29%)	F1-2 (22%), F3-4 (88%)	Sol (24), Mul (10)	NR	NR
Malik <i>et al</i> ^[4]	17	47-72	M (12), F (5)	OB (17), DM (12)	LC (17)	Sol (8), Mul (9)	1.1-8.0	LT (17)
Chagas <i>et al</i> ^[31]	7	35-77	M (4), F (3)	OB (7), DM (3), DL (2)	LC (6), Non-LC (1)	Sol (4), Mul (3)	2.8-5.2	Ope (2), PEI (1), TAE (3), LT (1)

HCC: Hepatocellular carcinoma; DM: Diabetes mellitus; OB: Obesity; DL: Dyslipidemia; LC: Liver cirrhosis; Mul: Multiple; Sol: Solitary; Ope: Surgical operation; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; TAE: Transarterial embolization; LT: Liver transplantation; NR: Not reported.

HCC patients with NASH-cirrhosis and with non-NASH-cirrhosis (HCV, HBV, alcoholic, CC, and otherwise). They concluded that patients with NASH and HCC have a good outcome after liver transplantation.

Giannini *et al*^[32] reported that patients with CC had a significantly greater prevalence of advanced HCC stage, lower amenability to any treatment, and shorter survival times compared with HCV patients, because HCC in CC patients is often diagnosed at an advanced stage owing to lack of surveillance.

MECHANISMS OF NASH-INDUCED HEPATOCARCINOGENESIS

Although the mechanism of carcinogenesis in patients with NASH remains uncertain, insulin resistance and oxidative stress may be involved in carcinogenesis of NASH.

NASH is characterized by insulin resistance with hyperinsulinaemia, and the resistance is thought to be involved in hepatocarcinogenesis. Insulin-like growth factor 1 (IGF-1)^[33] significantly activated mitogen-activated protein kinase (MAPK), and increased overexpression of the c-fos and c-jun proto-oncogenes in cultured hepatoma cells^[34].

Adiponectin and leptin are associated with insulin resistance. Severe liver steatosis and fibrosis were observed in adiponectin knockout (KO) mice as compared with wild type (WT) mice^[35]. Furthermore, liver adenoma and hyperplastic nodules developed in an adiponectin KO mouse, whereas no tumor was detected in WT mice. In animal models, leptin-mediated neovascularization,

which coordinated with VEGF, produced liver fibrosis and hepatocarcinogenesis in NASH^[36].

NASH-associated insulin resistance causes inhibition of hepatic mitochondrial fatty acid oxidation and increased intracellular fatty acids may lead to oxidative DNA damage by stimulating microsomal peroxidases^[37].

Oxidative stress may also promote carcinogenesis. Trans-4-hydroxy-2-nonenal, a major electrophilic by-product of lipid peroxidation caused by oxidative stress may be an important etiological agent for HCC *via* mutation at codon 249 of the *p53* gene^[38].

Reactive oxygen species (ROS) can activate fibrosis^[39]. Furthermore, the major products of lipid peroxidation, malondialdehyde, stimulates DNA mutations^[40]. Therefore, inflammation is a risk factor for various carcinomas^[41]. Oxidative stress has inactivated the expression of *Nrf1* gene that regulates gene transcription encoding enzymatic antioxidants. Recently, in an animal model, oxidative stress inactivation of the *Nrf1* gene in the liver has been reported to spontaneously produce HCC when oxidative injury was present before tumor formation^[42].

Ishii *et al*^[43] reported that in animal models, eicosapentaenoic acid (EPA) ameliorated steatohepatitis with decreasing serum ROS, which consequently inhibited development of HCC. Medical treatment with EPA may minimize the risk of HCC development in patients with NASH.

CONCLUSION

Most (91%) patients with NASH-associated HCC in our experience had been diagnosed with obesity, diabetes,

hypertension, or dyslipidemia. CC patients had these comorbid illnesses, and CC had clinical features consistent with NASH.

Occult HBV infection might be a possible etiologic agent of HCC, and the prevalence of past/occult HBV infection *via* positivity of HBc antibody in our cases was 27%. Negativity of HBc antibody is not necessarily a required item of diagnosis for NASH, and liver specimens of these HBc antibody positive patients had no histological features of chronic hepatitis B.

Although almost NASH-associated HCC was accompanied by liver cirrhosis according to previous reports^[1,17-19], the majority of our case series were accompanied by non-cirrhotic liver.

Furthermore, recent case reports^[2,30] about HCC arising from non-cirrhotic NASH have been accumulating. One possible explanation for this difference between our cases and other previous reports is that almost all patients with CC had clinical features consistent with NASH, but a diagnosis of NASH could not be confirmed by histology (likely “burnt out NASH”).

All cases of tumor recurrence in our series were observed within the first 2 years, no recurrence was observed after 2 years. These recurrence patterns of HCC suggested that the recurrence of HCC might be based on intrahepatic metastasis rather than multicentric carcinogenesis. NASH-associated HCC patients with non-curative treatments were not observed in our cases, because these patients did not receive liver biopsy or surgery. The existence of selection bias is unavoidable.

In conclusion, patients with non-cirrhotic NASH may be a high-risk group for HCC, and regular surveillance for HCC is necessary for non-cirrhotic NASH patients as well as cirrhotic patients.

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