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Case Report

Hepatocellular carcinoma in nonalcoholic fatty liver disease mimicking benign hemangioma: two case reports and literature review

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Abstract: Objective: To study the clinical features of nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC). Methods: The clinical manifestations, imaging features, pathological subtypes and treatment outcome of two cases with NAFLD-associated HCC were analyzed. Results: In these two cases, both were young, obese male patients, with contrast enhanced CT scan of hemangioma-like features. They had undergone surgical resection and both were reported as well-differentiated HCC pathologically. They were followed-up respectively up to 46 and 36 months post-operatively with no evidence of recurrence or metastasis. Conclusions: NAFLD-associated HCC has different radiological presentations from typical HCC. Incidental finding of any liver occupying lesions in NAFLD patients should raise immediate clinical attention.

Keywords: Non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma (HCC), Nonalcoholic steatohepatitis (NASH)

Introduction

According to the World Gastroenterology Organisation Global Guidelines, NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (>5% of hepatocytes histologically). A subgroup of NAFLD patients has liver cell injury and inflammation in addition to excessive fat, which is designated as nonalcoholic steatohepatitis (NASH) [1]. Oxidative stress, insulin resistance and genetic susceptibility play a critical role in the pathogenesis of NAFLD. The prevalence of NAFLD has doubled during last 20 years, whereas the prevalence of other chronic liver diseases has remained stable or even decreased. It is now the commonest liver disorder in the developed world affecting up to a third of individuals [2]. Although simple steatosis carries a relatively benign prognosis, a significant proportion of patients will progress to NASH related fibrosis and later cirrhosis with risk of HCC [3].

Two cases of NAFLD-associated HCC were encountered in China-Japan Friendship Hospital during the period from December 2010 to September 2011. The cases, together with a review of the oversea related literatures will be discussed below.

Case reports

Case 1

A 25 years old Chinese gentleman, who presented with an incidental finding of liver occupying lesion during medical checkup 2 months ago to the surgical outpatient department. He was asymptomatic and clinical examination was insignificant with body mass index (BMI) of 30.7. Otherwise, he was premorbidly healthy and denied history of alcoholic consumption.

He was warded on 9th, December 2010 and serial workup had been done. Abdominal ultrasonography showed fatty liver with heterogeneous liver echogenicity and two hypoechoic intrahepatic lesions were detected: the larger lesion was approximately 11.4 × 10.7 cm in size and the smaller lesion measured 3.5 × 3.0 cm. Contrast enhanced CT scan of the abdomen

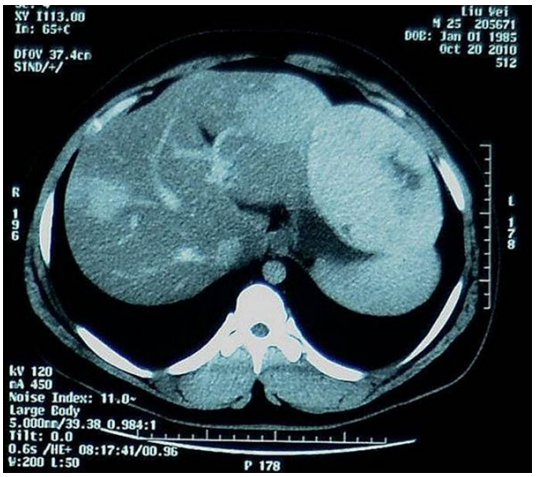

Figure 1. CT imaging of the liver in Case 1. The image shows liver hypodensity with exogenous infiltrating mass over left outer lobe, gradual centripetal contrast enhancement in delayed post contrast phase was observed; right lobe lesionwas isodense in enhancement.

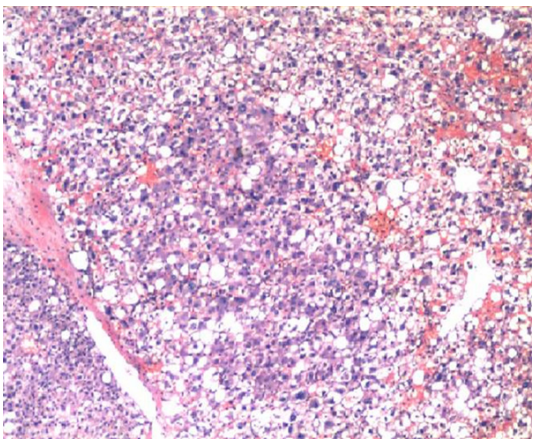

Figure 2. Hepatic histology of Case 1. Accumulation of fat vacuoles (steatosis) and well-differentiated tumor cells in hepatic lobule are seen.

revealed heterogeneous fatty liver and presence of space occupying lesions in left outer lobe and right lobe of the liver. Left outer lobe lesion demonstrated exogenous growing pattern, it showed patchy peripheral rim enhancement in hepatic arterial phase with gradual centripetal fill-in pattern during portal venous phase and the delayed-post contrast phase, which most likely suggestive of hemangioma. (**Figure 1**).

Laboratory investigation results: alpha fetoprotein (AFP), carcino-embryonic antigen (CEA) and CA 19-9 were within normal range; viral serology of hepatitis B and C were both non reactive; biochemically: Total Cholesterol (TC) 5.29 mmol/L, Triglyceride (TG) 4.05 mmol/L, Alanine aminotransferase (ALT) 60 U/L, Alkaline phosphatase (ALP) 246 U/L, Gamma-glutamyltranspeptidase (GGT) 138 U/L, others were insignificant; full blood count and coagulation profile were both within normal range.

Pre-operative impression was NAFLD with hemangioma of right and left outer lobe. Intraoperatively, the liver showed fatty liver appearance; an exogenous growing tumor occupying segment 2 and 3 was identified, it was firm in consistency and measured 10 cm in diameter; the macroscopic appearance of right hepatic lobe was otherwise insignificant. Surgical removal of tumor in the left outer lobe with intra-operative ultrasound guided resection of tumor in the right hepatic lobe was performed.

Post-operative histopathology examination (HPE) revealed severe fatty liver with well-differentiated hepatocellular carcinoma; immunochemical result: Hep (+), CEA (+), CK8/18 (+), CD34 (vessel +), CK7 (-), GPC-3 (-), EMA (-), AFP (-); special staining: Reticular fiber (+) (**Figure 2**).

He was counseled for extended hepatectomy after the review of his HPE result; however, he was not keen to go for a second operation. Since discharge, he has been followed up for 46 months till now, with no evidence of metastasis or recurrence for the time being.

Case 2

A 26 years old Chinese gentleman, who had also presented with the incidental ultrasound findings of liver occupying lesion 3 years ago during medical checkup and he was admitted to our ward in September, 2011. The lesion was approximately 6.0 × 7.0 cm in size, also with the initial impression of hemangioma. However, a repeated abdominal ultrasound 1 month prior to his admission reported a right hepatic hemangioma with its size had increased to 6.8 × 7.4 cm. Patient was otherwise asymptomatic and no significant findings clinically. His BMI was 30.5 and he denied any previous medical illness or any alcoholic consumption history.

Pre-operative abdominal ultrasonography showed heterogeneous fatty liver and uneven echo-

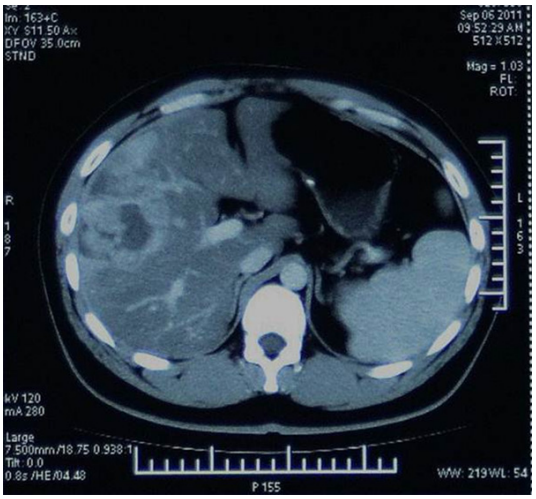

Figure 3. CT imaging of the liver in Case 2. It demonstrates liver hypodensity; presence of space-occupying lesion in right lobe with centripetal filling-up in the portal venous phase.

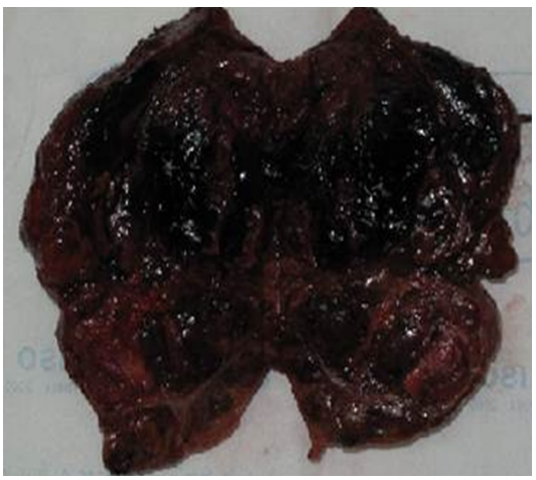

Figure 4. Liver gross specimen post surgical resection in Case 2. Intratumor hemorrhage was seen and its partial cross-sectional segment with grey-white appearance.

genicity in the right hepatic lobe, approximately 7.7 × 7.2 cm in size, which highly suggestive of hemangioma. Contrast enhanced abdominal CT scan demonstrated heterogeneous fatty liver and a space-occupying lesion in the right hepatic lobe with similar peripheral enhancement during arterial phase and progressive centripetal contrast enhancement during venous and delayed phase as mentioned earlier in the first patient (**Figure 3**). Laboratory investigation results: AFP, CEA and CA 19-9 were all within normal range; viral serology of hepatitis B and C were non reactive; Hepatitis B surface antibody (+); biochemically: TC 5.64 mmol/L, TG 3.18 mmol/L, ALT 101 U/L, Aspartate aminotransferase (AST) 48 U/L, GGT 111 U/L; full blood count and coagulation profile were within normal limit.

Pre-operative impression was NAFLD with right hepatic lobe hemangioma. Intra-operative findings revealed fatty liver with a tumor which occupied segment 5 and 8 of right anterior lobe, approximately 9.0 × 6.0 cm in size, soft in consistency with clear margin. Local surgical excision of the liver tumor was performed.

Dissection of the excised specimen revealed intratumoral hemorrhage with the dissected segment grey-whitish in appearance (**Figure 4**). Intraoperative frozen biopsy reported nodular liver cirrhosis, unable to rule out well-differentiated hepatocellular carcinoma with pending paraffin embedded biopsy result. Postoperative paraffin embedded biopsy revealed moderate to severe fatty liver with well-differentiated hepatocellular carcinoma; immunochemical findings: Hep (+), GPC-3 (focal +), CD 34 (vessel +), KP-1 (intratumor Kupffer cell +), Desmin (-), HMB45 (-), Melan-A (-), polyclonal S-100 (-), a-SMA -); special staining showed reticular (+), Manson (+). Patient had subsequently undergone a second operation of right hepatectomy with a good recovery and no metastasis or recurrence was reported after a 36 32 months' duration of follow-up so far.

Discussion

The prevalence of NAFLD in the general population of Western countries ranges from 20% to 30%, and it is much more prevalent in the obese group (80%-90%) [4]. Due to the variation in study methods and duration, the prevalence data of fatty liver disease in China showed a wide range between 0.6% and 30% [5]. In recent years, the prevalence of NAFLD has risen paralleling the increased in obesity, sedentary lifestyle and unhealthy dietary pattern and metabolic syndrome.

Liver cirrhosis is the most important risk factor for HCC. Studies have shown that 80% of patients with HCC were associated with liver cirrhosis of various causes (including: HCV or HBV -related cirrhosis, alcoholic cirrhosis and idiopathic cirrhosis) [6], and most cryptogenic

cirrhosis may be NASH related [7]. Torres et al. reported that HCC may occur in NASH patient without a background of cirrhosis. The typical noncirrhotic NASH patient who presents with HCC appears to be older, predominantly male and meets criteria for one or more features of metabolic syndrome, including obesity, type 2 diabetes mellitus, hypertension or hyperlipidaemia [8].

Both patients reported in our study were young, obese male patients with underlying hyperlipidaemia, but non-hypertensive or diabetic. Their pre-operative imaging, intra-operative findings and post-operative pathological study had all shown no evidence of liver cirrhosis, which is consistent with Torres et al. review that NAFLD patient may develop HCC without progressing to cirrhotic stage. The exact mechanism behind the development of HCC in NASH remains unclear; although the pathophysiological mechanisms behind the development of NASH related to insulin resistance and its subsequent inflammatory cascades likely contribute to the carcinogenic potential of NASH. Patients with obesity or diabetes, are not only associated with significant risk for development of NASH and disease progression, but also predispose themselves to the development of various cancers, including HCC [7].

Insulin resistance associated with obesity, metabolic syndrome and diabetes leads to increase release of free fatty acid by adipose cells and also release of multiple pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), NF-κB, etc. These processes favor the development of hepatic steatosis and inflammation in the liver; and also induce the occurrence of HCC [17]. Petta et al. demonstrated that these cytokines leads to hepatocyte death, compensatory hepatic proliferation, and ultimately carcinogenesis via a complex molecular interplay [9].

Adiponectin is an anti-inflammatory polypeptide secreted by adipocytes, and it inhibits tumorigenesis by inhibiting angiogenesis via modulation of apoptosis. However, adiponectin is decreased in those with insulin resistant. Hyperinsulinemia up-regulates the production of insulin like growth factor-1 (IGF-1), a peptide hormone which stimulates growth through intrahepatic cellular proliferation and inhibition of apoptosis within the liver [10]. Insulin also activates insulin receptor substrate-1 (IRS-1), which is involved in cytokine signaling pathways and has been shown to be up regulated in HCC patients. In NASH, the activation of carcinogenic inflammatory cytokines and signal pathway with the reduction of tumor suppressor factor may be closely associated with the occurrence of HCC.

In addition, the development of NASH is also associated with oxidative stress and the release of reactive oxygen species (ROS) which likely contributes to the development of HCC. An insulin resistant animal model showed that ROS production is increased in mitochondria of hepatocytes with fatty infiltration [7]. The oxidative stress may promote carcinogenesis through steatosis, inflammation and cell proliferation; it may also directly induce cancer-promoting mutations.

Pre-operative contrast-enhanced computed tomography imaging of the two cases in our study had both demonstrated peripheral enhancement in early phase, with gradual centripetal contrast enhancement during portal venous phase and the delayed post contrast phase. These presentations were in keeping with the characteristic features of hemangioma rather than a typical imaging finding of HCC. Therefore, both cases were initially diagnosed probably hemangioma, but subsequently confirmed as HCC histopathologically. Comparative study is needed to evaluate any significant difference in imaging features of NAFLD-associated HCC from typical HCC and its specificity. Both our NAFLD patients had developed well-differentiated HCC without the background of liver cirrhosis. Effect of pathogenetic mechanism of NAFLD, such as steatosis, ballooning degeneration, liver regeneration and repair etc., to the atypical imaging presentations of NAFLD-associated HCC has yet to be established. On the other hand, it shall also be differentiated from fibrolamellar hepatocellular carcinoma which is mostly encountered in young population.

Current treatments of HCC chiefly include hepatectomy, orthotopic liver transplantation, transcatheterarterial chemoembolization, ethanol injection and radio frequency ablation.

Takuma et al. had 11 cases of NASH-associated HCC, whom had all undergone radical treat-

ments, including radical surgical resection (7 cases), radiofrequency ablation (3 cases) and microwave coagulation therapy (1 case), their post-operative recurrence-free survival rate were 72% in 1 year, 60% in 3 years and 60% in 5 years [12].

Malik et al. had 17 cases of NASH-associated HCC underwent liver transplantation with 2.5 years survival rate post-operatively of 88%, among which 5 cases were moderate to well differentiated tumor, 11 cases of moderately differentiated and 1 case of poor differentiated HCC [13].

Hashizume et al. reported 9 cases of NASH associated HCC, in which 6 cases underwent surgical resection, 2 cases of radiofrequency ablation and 1 case of palliative arterial chemoembolization; all with no recurrence after average follow-up period of 32.1 months in 8 cases, excluding the one who had received palliative arterial chemoembolization therapy. Post-operative pathological study of the 6 cases post-surgical resection revealed well-differentiated tumor in 1 case, moderately differentiated in 4 cases and poorly differentiated in 1 case [14].

Tokushiqe et al. prospective study of the prognosis between NASH-associated HCC and HCV associated HCC concluded that NASH-associated HCC had a 5 years survival rate of 55.2% and a 5 years accumulative recurrence rate of 69.8%, which are similar to the result of HCV associated HCC and the recurrence are mostly multifocal [15].

Reddy et al. study in 52 cases of NASH-associated HCC and 162 cases of HCV or alcoholic associated HCC, with all underwent radical treatment (including liver transplantation, surgical resection and radiofrequency ablation), reported no significant difference in recurrent-free survival period in between NASH associated HCC and HCV or alcoholic associated HCC. In addition, both the groups had no significant difference in the degree of tumor differentiation (well differentiated, moderate differentiated and poor differentiated tumor were respectively: 26.1% Vs 14.8%, 63% Vs 66%, 10.9% Vs 17.7%, *p* value: 0.241) [16]. The study showed that NASH associated HCC patient had similar pathological patterns as compared to other chronic liver disease associated HCC. The survival rate and the recurrence rate after radical therapy in NASH-associated HCC are similar to those with other liver disease associated HCC. Both cases in our study were reported as well-differentiated tumor pathologically, with no evidence of recurrence or metastasis after 46 months and 36 months of post-operative follow-up respectively.

The incidence of HCC in patients with NAFLD is rising with the increasing prevalence of NAFLD, especially in developed countries with the growing epidemics of obesity and diabetes. Because of the long, indolent clinical course of NAFLD, patients with significant disease may be overlooked. Therefore, immediate clinical attention shall be drawn to NAFLD patients with detection of any liver occupying lesions during screening. Early surgical intervention of potentially malignant lesions should be considered in order to secure a better prognosis. Further study about the imaging characteristics of NAFLD-associated HCC and availability of any more specific investigation has yet to be carried out.

Disclosure of conflict of interest

None.

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