Diagnosis of Icteric-Type Hepatocellular Carcinoma by Fine Needle Aspiration

A Case Report

Jee-Fu Huang, M.D., **Shinn-Cherng Chen,** M.D., Ph.D., **Liang-Yen Wang,** M.D., Ph.D., **Ming-Lung Yu,** M.D., Ph.D., **Chia-Yen Dai,** M.D., Ph.D., **Wan Long Chuang,** M.D., Ph.D., and **Wen-Yu Chang,** M.D., Ph.D.

Background

Bile duct invasion is very rare in patients with hepatocellular carcinoma (HCC). It usually presents difficult problems with the clinical differential diagnosis. Moreover, another difficulty might arise when an obstructive jaundice patient is found to have past history of 2 separate malignancies. Fine needle aspiration (FNA) becomes the method of choice for clarification of the bile duct tumor thrombus.

Case

A 72-year-old man presented with progressive obstructive jaundice for 1 month. Past history revealed the occurrence of 2 distinct malignancies during the previous 3 years; they had been resected successfully. Initial imaging studies, including abdominal sonography and computed tomography, were negative for the liver. However, FNA demonstrated clusters of pleomorphic and hyperchromatic cancer cells with an increased nuclear/cytoplasmic ratio proliferating in a vague trabecular pattern with some appearance of sinusoids. Multinucleated giant cells were seen. No bile duct epithelial cells were seen. The diagnosis of the third separate malignancy, moderately differentiated HCC, was made.

Conclusion

To our knowledge, this is the first report of icteric-type HCC diagnosed by FNA although the primary lesion was undetectable on routine, noninvasive examinations. FNA cytology is an accurate and minimally invasive method for early confirmation of biliary HCC thrombi. (Acta Cytol 2006;50:531–533)

Keywords: aspiration biopsy, fine-needle; icteric type hepatocellular carcinoma.

FNA cytology examination can be an accurate and minimally invasive method for early confirmation of bile duct tumor thrombus.

Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver and also the most prevalent cancer in Taiwan. Clinically it presents in diverse ways, probably due to its different biologic characteristics. Obstructive jaundice caused by HCC thrombi is a rare clinical manifestation. Such a presentation of HCC has been defined as icteric-type HCC (IHCC).[1] The incidence of IHCC has been reported to be 0.53–9%.[1-3] Many diagnostic modalities, including tumor markers, imaging and histopathology, can be easily applied in clinical practice because such cases usually coexist with an advanced primary liver lesion or vessel invasion.[4,5] Percutaneous fine needle aspiration (FNA) has been shown to be an easy-to-perform, accurate and minimally invasive technique for obtaining a tissue diagnosis in space-occupying lesions of the liver. It has been a pivotal tool in the diagnosis of HCC for decades due to its high accuracy and clinical benefits.[6,7]

However, clinicians would be confused when facing an obstructive jaundice patient with not only a bile duct tumor but also a past history of 2 malignancies with separate origins. Moreover, primary liver tumor is not identified with initial noninvasive tools, abdominal sonography and computed tomography (CT). It raises great difficulty with the clinical differential diagnosis.

Case Report

A 72-year-old, diabetic man presented with progressive jaundice, fatigue and anorexia for 1 month. There was no history of alcohol use, intravenous drug use or transfusions. The family history was not contributory. The patient had undergone an operation for a buccal tumor 3 years earlier, and pathologic study disclosed an oral squa-

From the Departments of Internal Medicine, Fooyin University Hospital, Pingtung, and Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, R.O.C.

Dr. Huang is Assistant Professor, Department of Internal Medicine, Fooyin University Hospital.

Drs. Chen, Wang and Yu are Associate Professors, Department of Internal Medicine, Kaohsiung Medical University Hospital.

Dr. Dai is Assistant Professor, Department of Internal Medicine, Kaohsiung Medical University Hospital.

Dr. Chuang is Professor, Department of Internal Medicine, Kaohsiung Medical University Hospital.

Dr. Chang is Professor, Department of Internal Medicine, Kaohsiung Medical University Hospital.

Address correspondence to: Wen-Yu Chang, M.D., Ph.D., Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Shih-Chuan first Road, Kaohsiung City, Taiwan, R.O.C. (jeefuhuang@yahoo.com.tw).

Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

Received for publication October 1, 2004.

Accepted for publication May 24, 2005.

mous cell carcinoma of well-differentiated type. Anemia and gross hematuria developed 1 year earlier. Serial urologic examinations showed a left ureteral tumor with bleeding. Left nephrouretectomy was performed then, and pathology revealed transitional cell carcinoma. Thereafter the patient received regular follow-up in an out-

Attention must be paid to multiple primary malignancies since some of these malignancies are predicted to overlap....

patient clinic.

On physical examination, the patient was afebrile and markedly icteric, with no sign of cirrhosis. His abdomen was soft with some right upper quadrant pain with no rebound tenderness. There was no ascites or pretibial edema. A 2-finger breadth of liver margin was palpable below the right costal area. The liver surface was smooth and spleen not palpable.

The serum total bilirubin level was 7.4 mg/dL. Other liver function tests were as follows: ALT 45 IU/L, AST 11 IU/L, alkaline phosphatase 636 IU/L and gamma-glutamyl transferase 422 IU/L. Alpha-fetoprotein was 7.1 ng/mL (normal, <20), and carcinoembryonic antigen was 4.0 ng/mlL (normal, <2.5). Both HBsAg and anti-HCV antibody were negative. The hematologic values were: red blood cells $285\times10^4/mm^3$, hemoglobin 8.8 g/dL, platelets $45\times10^4/mm^3$ and white blood cells $8{,}880/mm_3$.

Abdominal sonography showed an isoechoic to hypoechoic tumor located in the common bile duct. Dilatation of bilateral intrahepatic ducts and common hepatic duct was seen (Figure 1). There was no other lesion detected in the liver parenchyma on sonography or CT. Sonographically guided (SSA-250A, Toshiba Corp., Tokyo, Japan) FNA was carried out using a 15-cm-long, 22-gauge Chiba needle (Top Corp., Tokyo, Japan) and 3.75-MHz linear puncture probe (Toshiba). Since the cytologic diagnosis disclosed HCC, transcatheter arterial chemoembolization (TACE) was performed on the second day. An HCC measuring 1.5 cm in diameter was detected in segment 2 within the liver on angiography. The bile duct tumor thrombus decreased in size gradually on follow-up imaging studies. The total bilirubin levels then decreased to 3.2

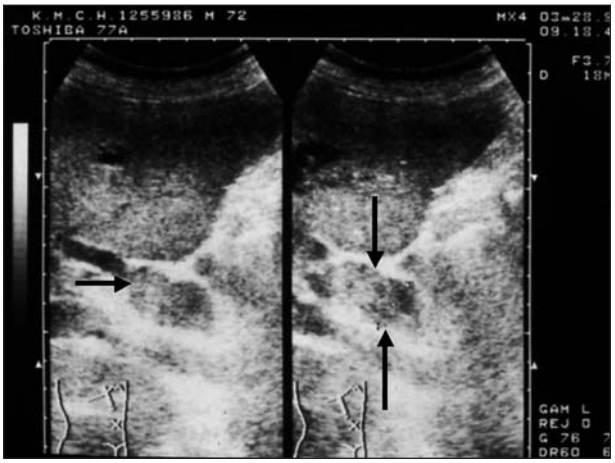

Figure 1 Abdominal sonography. Isoechoic to hypoechoic tumor (arrows) located within the common bile duct. Dilatation of intrahepatic ducts is also shown.

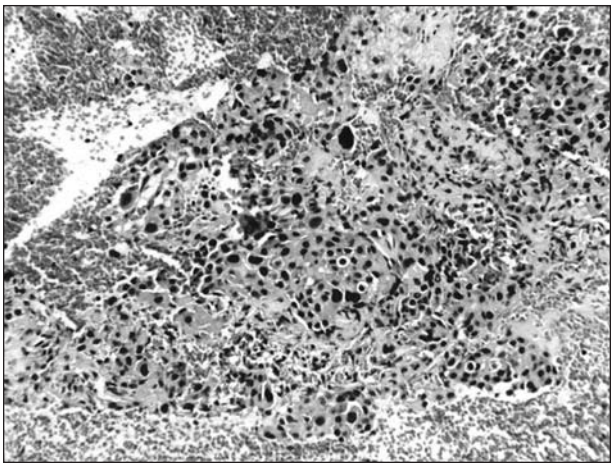

Figure 2 The tumor cells proliferate in a vaguely trabecular pattern with some appearance of sinusoids. Cell pleomorphism and hyperchromaticism are seen with increased N/C ratio. Multinucleated giant cells are present. No bile duct epithelial cells are seen. Moderately differentiated HCC was considered (cell block, H-E, ×275).

and 1.4 mg/dL 1 week and 10 days after TACE, respectively. The patient died of advanced liver failure and cholangitis due to multiple intrahepatic metastases 12 months after TACE.

The aspirated, noncohesive, bloody sample was smeared on glass slides and wet fixed in 95% ethanol at once, then stained with both hematoxylin-eosin (H-E) and Papanicolaou stain for cytologic examination. The remaining aspirated tissue fragments were collected in a tube of 10% neutral-buffered formalin and processed for cell block histology using 2% agarose to hold the tissue, followed by paraffin embedding. H-E was applied to the cell block sections. On cytopathologic examination, it displayed extreme hypercellularity with 3-dimensional fragments. The tumor cells proliferated in a vaguely trabecular pattern. Sinusoids were demonstrated. Pleomorphic and hyperchromatic cancer cells with an increased nuclear/cytoplasmic (N/C) ratio were seen. Multinucleated giant cells were also present. No bile duct epithelial cells were seen. Moderately differentiated HCC was considered (Figure 2).

Discussion

Obstructive jaundice is the initial complaint in 1–12% of patients with HCC.[8,9] Most of the patients have poor liver reserve function and advanced tumor stage. Most hepatologists in Western countries are not familiar with this rare variety of HCC because they have little chance to see it. Mallory et al[10] described the first case in 1947, in which HCC invaded the cystic duct and gave rise to obstructive jaundice caused by hemobilia from the tumor thrombi. In 1975, Lin[1] first named the tumor icteric-type hepatoma, which manifested as obstructive jaundice in the early stage before the tumor became discernible or palpable. Thereafter, there have been few and scattered reports of such presentations of HCC in the English-language literature.[5,11,12] The previous reports were made mainly from operative findings or autopsy because most of the cases were often incorrectly regarded as bile duct carcinoma, blood clots, stones or polyps.[3,11,12] It has also been reported that IHCC may occur in patients even with no primary detectable lesion.[13,14] It is at a very advanced stage when HCC emerges with biliary invasion, and it usually carries a very poor prognosis.[2,5] If no urgent treatment strategies are implemented after early diagnosis, most of these patients will die soon. Cholangitis secondary to tumor obstruction is

the major cause of death in these patients.

Past history revealed that our patient had had 2 distinct primary cancers before. Meanwhile, both viral hepatitis and tumor markers were normal, and there was no evidence of liver cirrhosis. Although rare, IHCC suggests the possibility that the bile duct tumor thrombus might be a metastatic lesion from either of the 2 primary origins. However, bile duct primary cancer, cholangiocarcinoma, had also been listed in the initial differential diagnosis. Noninvasive imaging modalities, abdominal sonography and CT, can be used for initial clarification. However, there was no liver tumor detectable on these routine imaging studies in this patient. Under these somewhat clouded circumstances, sonographically guided FNA is the most efficient and easy way to make an early diagnosis. The tissue obtained can be examined immediately with cytologic stains or fixed pathologic processes. To our knowledge, this is the first report on an IHCC case diagnosed by FNA although the primary lesion was undetectable on routine sonography and CT.

Most HCC can be discerned cytologically by using the following criteria: absence of epithelial cells, presence of bile, high cellularity, trabecular growth with a tendency for cell dissociation, increased N/C ratio, naked and atypical nuclei, and multinucleated giant cells.[6,7] Generally, it is not difficult to distinguish HCC from cholangiocarcinoma because the latter usually shows microglandular arrangement and clusters of cells resembling normal bile duct epithelium. The cytomorphologic findings on H-E and Papanicolaou stain in this case were easily demonstrated to be moderately differentiated HCC. However, some difficulty in cytologic diagnosis arises in separating less-differentiated HCC from metastatic cancers or other unusual tumors. Resolution of the issue lies with the recognition of obvious cancer cells of hepatocytic origin since metastatic carcinoma and cholangiocarcinoma may simulate HCC in part, leading to difficulty with the interpretation of aspirates from the bile duct tumor thombus. Moreover, poor preservation of architecture during cytologic preparation somewhat limits specificity. Therefore, besides the various cytomorphologic criteria most frequently used, the appearance of sinusoid, bile and cytoplasmic vacuolation should be evaluated in cell block processing in case of controversy. The features of cell block preparations with H-E in this case were well demonstrated to be consistent with the initial cytomorphologic findings. Cytologic smears and cell block sections with H-E provided a rapid and accurate diagnosis in our patient within a few hours.

Noteworthy is that our patient had 3 distinct histologic types of malignancies over 3 years. The mechanism of carcinogenesis leading to triple cancers from 3 distinct origins is obscure. Warren and Gates[15] defined 3 diagnostic criteria for multiple primary malignant tumors: (1) each of the tumors must present a definite picture of malignancy, (2) each must be distinct, and (3) the probability that 1 is metastatic from the other must be excluded. The clinical manifestations in our patient fulfilled those criteria. It has been shown that the incidence of extrahepatic malignancies associated with HCC, whether synchronously or metachronously, is 6.8–10.1%.[16,17] Certain states of immunodeficiency or genetic defects might be deduced. Attention must be paid to multiple primary malignancies since some of these malignancies are predicted to overlap, and the percentage of overlapped neoplasms is increasing.[18] This case suggests the need to maintain an open mind when investigating cancer patients.

In conclusion, FNA cytology examination can be an accurate and minimally invasive method for early confirmation of bile duct tumor thrombus.

References

1. Lin TY: Tumors of the liver. *In* Bockus Gastroenterology. Philadelphia, WB Saunders, 1976, pp 522–533
2. Huang JF, Wang LY, Lin ZY, Chen SC, Hsieh MY, Chuang WL, Yu MY, Lu SN, Wang JH, Yeung KW, Chang WY: Incidence and clinical outcome of icteric type hepatocellular carcinoma. J Gastroenterol Hepatol 2002;17:190–195
3. Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N, Nakashima T: Hepatocellular carcinoma presenting as intrabile duct tumor growth: A clinicopathologic study of 24 cases. Cancer 1982;49:2144–2147
4. Okuda K, Kubo Y, Okazaki N, Arishima T, Hashimoto M: Clinical aspects of intrahepatic bile duct carcinoma including hilar carcinoma. Cancer 1977;39:232–246
5. Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, Yamamoto N, Iimuro Y, Shimahara Y, Yamaoka Y: Clinicopatholgic evaluation of hepatocellular carcinoma with bile duct thrombi. Surgery 2000;127:779–783
6. Kuo FY, Chen WJ, Lu SN, Wang JH, Eng HL: Fine needle aspiration cytodiagnosis of liver tumors. Acta Cytol 2004;48:142–148
7. Das DK: Cytodiagnosis of hepatocellular carcinoma in fine-needle aspirates of the liver: Its differentiation from reactive hepatocytes and metastatic adenocarcinoma. Diagn Cytopathol 1999;21:370–377
8. Kew MC, Paterson AC: Unusual clinical presentations of hepatocellular carcinoma. Trop Gastroenterol 1985;6:10–22
9. Okuda K: Clinical aspects of hepatocellular carcinoma: Analysis of 134 cases. *In* Hepatocellular Carcinoma. Edited by K Okuda, RL Peters. New York, John Wiley, 1976, pp 387–436
10. Mallory TB, Castleman B, Parris EE: Case records of the Massachusetts General Hospital. N Engl J Med 1947;237:673–676
11. Roslyn JJ, Kuchenbecker S, Longmire WP, Tompkins RK: Floating tumor debris: A cause of intermittent biliary obstruction. Arch Surg 1984;119:1312–1315
12. Terada T, Nakanuma Y, Kawai K: Small hepatocellular carcinoma presenting as intrabiliary pedunculated polyp and obstructive jaundice. J Clin Gastroenterol 1989;11:578–583
13. Buckmaster MJ, Schwartz RW, Carnahan GE, Strodel WE: Hepatocellular carcinoma embolus to the common hepatic duct with no detectable primary hepatic tumor. Am Surg 1994;60: 699–702
14. Cho HG, Chung JP, Lee KS, Chon CY, Kang JK, Park IS, Kim KW, Chi HS, Kim H: Extrahepatic bile duct hepatocellular carcinoma without primary hepatic parenchymal lesions. Korean J Int Med 1996;11:169– 174
15. Warren S, Gates O: Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer 1932; 16:1358–1414
16. Onitsuka A, Hirose H, Ozeki Y, Hino A, Senga S, Iida T: Clinical study on hepatocellular carcinoma with extrahepatic malignancies. Int Surg 1995;80:128–130
17. Imada J, Hoshino H, Nishimura D, Morita K, Yoshida N, Katada N, Sano H, Kato K, Mori N: Case report: Multiple cancers: Hepatocellular carcinoma and adenocarcinomas of the common bile duct and the gallbladder in a woman with primary biliary cirrhosis. J Gastroenterol Hepatol 1996;11:546–550
18. Murate T, Takagi E, Shimokata K: Simultaneously diagnosed triple primary neoplasms: A case report. Jpn J Cancer Clin 1989;35:741–747