

Metastatic Hepatocellular Carcinoma in the Urinary Bladder with Radiation-induced Hemorrhagic Cystitis

Shiu-Dong Chung,^{1,2} Chen-Hsun Ho,² Shun-Fa Hung,² Huai-Ching Tai,² Hong-Jeng Yu,²
Kuo-How Huang^{2*}

Metastatic hepatocellular carcinoma (HCC) to the urinary bladder is very rare. We present the case of a 58-year-old female patient who was diagnosed to have both HCC and cervical cancer. She developed hemorrhagic cystitis 2 years after radiation therapy for cervical cancer. During endoscopic electrocauterization for hemorrhagic cystitis, three small reddish tumors measuring less than 1 cm in diameter and with a raspberry-like appearance were found. Transurethral bladder tumor resection was performed. Pathology confirmed metastatic HCC to the bladder. Due to the similar appearance, these tumors are liable to be misinterpreted as engorged vessels secondary to irradiation if biopsies are not taken. Differential diagnosis by pathology is mandatory for such patients. [*J Formos Med Assoc* 2007;106(10):861–863]

Key Words: bladder neoplasm, hemorrhagic cystitis, hepatocellular carcinoma, radiation

Hematogenous spread of hepatocellular carcinoma (HCC) has poor prognosis and common sites of metastasis include lung, bone, adrenal glands and brain.¹ To our knowledge, only three cases of metastatic bladder HCC have been reported in the literature.^{2–4} We report an unusual case of metastatic bladder HCC, which coexisted with radiation-induced hemorrhagic cystitis.

Case Report

A 58-year-old woman with chronic hepatitis C-related liver cirrhosis was diagnosed to have a small HCC 3 years ago. She refused any treatment. A year later, she was also diagnosed to have cervical cancer and radiation therapy was administered. Her condition was stable in the following 2-year period.

She then presented to the urology outpatient clinic with a 2-month history of intermittent and painless gross hematuria. Physical examination revealed icteric sclera and distended abdomen with shifting dullness. Urine cytology was negative for malignancy. Urinalysis showed more than 100 red blood cells per high power field. Hemogram revealed severe anemia and thrombocytopenia (hemoglobin, 4.9 g/dL; red blood cell count, $1.71 \times 10^6/\mu\text{L}$; platelet count, $5.9 \times 10^4/\mu\text{L}$). Biochemistry showed abnormal liver function (total bilirubin, 4.64 mg/dL; alanine aminotransferase, 224 U/L), hypoalbuminemia (serum albumin, 2.5 g/dL) and high α -fetoprotein (> 85,000 ng/mL).

After component blood transfusion, cystoscopic examination was performed and revealed diffuse hyperemic bladder mucosa and engorged vessels with active bleeding, consistent with radiation-induced hemorrhagic cystitis. In addition, three

©2007 Elsevier & Formosan Medical Association

¹Department of Urology, Far-Eastern Memorial Hospital, Ban Ciao, and ²Department of Urology, National Taiwan University Hospital, Taipei, Taiwan.

Received: December 4, 2006
Revised: January 27, 2007
Accepted: March 13, 2007

***Correspondence to:** Dr Kuo-How Huang, Department of Urology, National Taiwan University Hospital, 7 Chung Shan South Road, Taipei 100, Taiwan.
E-mail: harry@ha.mc.ntu.edu.tw

reddish, raspberry-like tumors measuring less than 1 cm in diameter were identified on the posterior wall of the urinary bladder (Figure 1). The engorged vessels with active bleeding were electrocauterized. The bladder tumors were resected by transurethral tumor resection (TUR-BT).

Pathology demonstrated tumor cells with abundant eosinophilic cytoplasm, round vesicular nuclei and prominent nucleoli, arranged in a trabecular pattern intervened by sinusoid vessels (Figure 2A). The depth of invasion displayed submucosal involvement. Immunohistochemical study of the tumor cells revealed diffuse positivity

for Hep-Par-1 (Figure 2B) and weak positivity for cytokeratin-7. The diagnosis of metastatic bladder HCC was confirmed.

After TUR-BT, abdominal and pelvic computed tomography showed liver cirrhosis with remarkable esophageal varices and ill-defined hypodense lesions in both hepatic lobes. Portal vein thrombosis could also be identified. Recurrent HCC was impressed. She refused further treatment and was lost to follow-up. She died of disseminated HCC metastasis and cachexia 5 months after TUR-BT without adjuvant treatment.

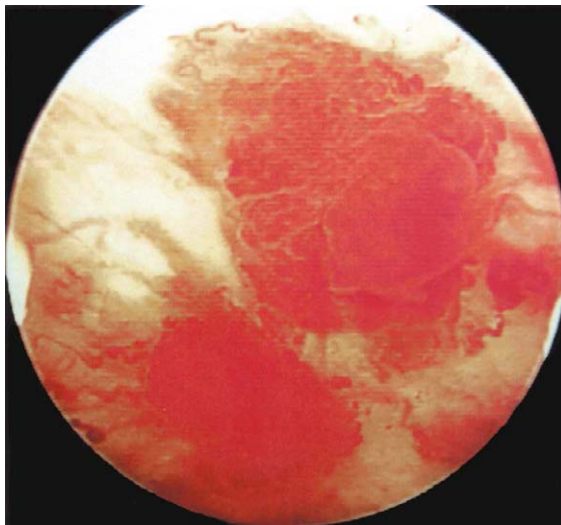


Figure 1. Reddish and flat tumors mimicking engorged vessels on the posterior wall of the bladder.

Discussion

HCC is the fifth most common cancer in the world. The prevalence of HCC and mortality from it in Taiwan are higher than in the West.⁵ Extrahepatic metastases are an indicator of poor prognosis. Common sites of HCC metastases are lung, bone, adrenal glands, and brain.¹ Franks et al reported the first case of bladder HCC who survived for more than 2 years after being treated with combined transurethral resection and systemic chemotherapy.² Compared with the reported case, our case had a shorter survival period in the absence of systemic chemotherapy. The two other reported cases had ominous prognosis without adjuvant therapy. However, the exact prognosis and optimal

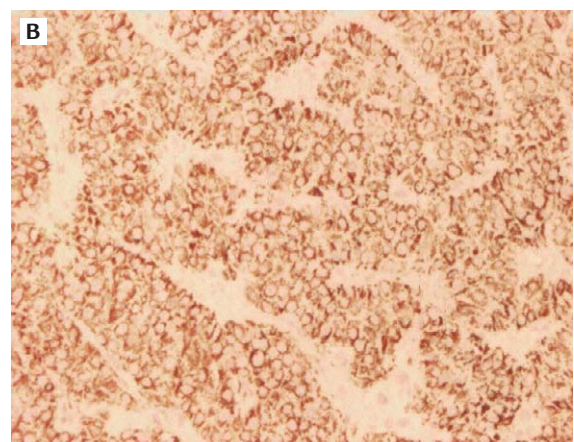
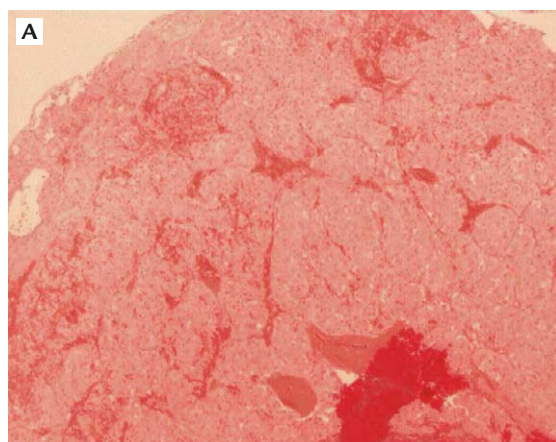


Figure 2. (A) Microscopically, the tumors are composed of large round cells with abundant eosinophilic cytoplasm, round vesicular nuclei and prominent nucleoli. The tumor cells are arranged in a trabecular pattern intervened by sinusoid vessels with submucosal invasion (hematoxylin & eosin, 100×). (B) Immunohistochemical staining shows diffuse Hep-Par 1 positivity in the cytoplasm of the tumor cells (ABC method, 100×).

modality of treatment for metastatic bladder HCC remain unclear due to its rarity.

In addition to its rarity, our case is unique because the metastatic bladder HCC co-existed with radiation-induced hemorrhagic cystitis. Radiation-induced hemorrhagic cystitis may occur in later years to decades after radiation therapy, and the predominant symptom is hematuria, which can be managed by transurethral electrocauterization. It has also been reported that the risk of bladder urothelial carcinomas will increase following radiotherapy for prostate cancer and cervical cancer. The typical gross appearance of radiation cystitis on cystoscopic examination is diffuse hyperemic bladder mucosa and engorged vessels. The differential diagnosis between radiation cystitis, urothelial carcinoma, and metastatic HCC is difficult due to the similar gross appearance. For intractable cases with radiation-induced hemorrhagic cystitis, hyperbaric oxygen therapy has been reported to have promising outcomes.⁶ However, it is controversial to apply this therapy to patients with residual malignancy because of the potential for cancer proliferation.⁷ Thus, it is mandatory to be sure of the origin of bladder lesions before hyperbaric oxygen therapy. All urologists should bear in mind that malignant bladder lesions might be

misinterpreted as engorged vessels secondary to irradiation if a biopsy for pathologic proof has not been undertaken.

References

1. Katyal S, Oliver JH, III, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000;216:698–703.
2. Franks ME, Konety BR, Bastacky S, Gritsch HA. Hepatocellular carcinoma metastatic to the bladder after liver transplantation. *J Urol* 1999;162:799–800.
3. Al-Brahim N, Alowami S, Davis I, Daya D. Synchronous transitional cell carcinoma and metastatic hepatocellular carcinoma in the urinary bladder: a case report. *Can J Urol* 2004;11:2463–6.
4. Kurimoto S, Komatsu H, Doi N, Wakumoto Y, Tominaga T, Nishimura Y. Metastasis of hepatocellular carcinoma to the urinary bladder. *Urologe A* 1993;32:64–5.
5. Lee CL, Hsieh KS, Ko YC. Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. *Cancer Epidemiol Biomarkers Prev* 2003;12:57–9.
6. Neheman A, Nativ O, Moskovitz B, Melamed Y, Stein A. Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis. *BJU Int* 2005;96:107–9.
7. Bradfield JJ, Kinsella JB, Mader JT, Bridges EW. Rapid progression of head and neck squamous carcinoma after hyperbaric oxygenation. *Otolaryngol Head Neck Surg* 1996; 114:793–7.