Extrahepatic metastasis of hepatocellular carcinoma arising from a hepatic adenoma without concurrent intrahepatic recurrence

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ABSTRACT

Hepatocellular carcinoma (HCC) arising from a hepatic adenoma is a rare phenomenon accounting for fewer than 5% of HCC cases; it seldom recurs after resection of the primary tumour. We report a case of extrahepatic metastasis of HCC arising from a hepatic adenoma that presented as a solitary sternal metastasis without any evidence of intrahepatic recurrence.

Our patient was initially treated with radiation therapy and bland embolization, without response. Subsequently, the patient developed progressive disease while taking sorafenib. He later received chemotherapy with docetaxel and gemcitabine, with the development of multiple pulmonary and splenic nodules. However, he remained free of intrahepatic recurrence. To the best of our knowledge, this is the first case of extrahepatic metastasis of HCC arising from a hepatic adenoma without evidence of intrahepatic recurrence.

Key Words Hepatocellular carcinoma, sternal metastasis, hepatic adenoma, extrahepatic recurrences

INTRODUCTION

Hepatic adenomas are benign neoplasms of the liver that lack normal hepatic architecture. They are usually rare in men, primarily affecting women of reproductive age who have a history of oral contraceptive pill use and people with exposure to androgens or anabolic steroids. Malignant transformation of hepatic adenoma into hepatocellular carcinoma (HCC) is reportedly rare, and its pathophysiology is not fully understood.

Hepatocellular carcinoma commonly develops in the background of cirrhosis. Compared with intrahepatic recurrence, extrahepatic metastasis is relatively low in incidence, but has a worse prognosis. The most common sites of extrahepatic metastasis are lungs, lymph nodes, bones, and adrenal glands. When HCC metastasizes to bone, it most commonly involves the vertebrae, ribs, and long bones. In the English literature, only 5 cases of HCC metastatic to the sternum have been reported.

Here, we report the case of a patient with hepatic adenoma that transformed to HCC, with an extrahepatic metastasis to the sternum 2 years after the initial diagnosis.

CASE PRESENTATION

A 75-year-old white man presented with abdominal pain and an epigastric mass. Computed tomography (CT) imaging of abdomen and pelvis showed a left-sided hepatic lesion in hepatic segment IVa/III. He had no prior history of androgen steroid use, heavy alcohol use, hepatitis, blood transfusions, tattoos, intravenous drug use, or any family history of liver disease. Serologic evaluation for hepatitis B and C was negative. Ultrasound-guided biopsy of the hepatic lesion was consistent with HCC.

A left hepatic lobectomy revealed a moderately differentiated HCC surrounded by a hepatic mass with increased cellular density compared with the non-neoplastic liver parenchyma. Two components were identified in this mass, including a hepatocellular adenoma (HCA) composed of bland hepatocytes with normal thickness of hepatic cell plates and naked arteries. Figure 1(A,B) shows the transition of HCA to HCC.

Immunohistochemistry was performed using antibodies against glypican 3 (clone G12: Cell Marque Corporation, Rocklin, CA, U.S.A.) and CD34 (clone QBEnd/10: Ventana...
Medical Systems, Tucson, AZ, U.S.A.), beta-catenin (clone 14: Ventana Medical Systems), and glutamine synthetase (clone 6 glutamine synthetase aa. 1-373: BD Biosciences, San Jose, CA, U.S.A.). Figure 2 shows the immunoreactivities of the four antibodies in the tumour, with transition from hca [Figure 2(A–D), left panel] to hcc [Figure 2(A–D), right panel]. Glypican 3 was negative in both hca and hcc [Figure 2(A)]. CD34 showed a diffuse sinusoidal staining pattern in both hca and hcc [Figure 2(B)]. The nuclear staining of beta-catenin was positive in few cells of hca; they were positive in much higher numbers in the hcc cells [Figure 2(C)]. Glutamine synthetase was diffusely positive in both the hca and hcc components [Figure 2(D)].

The patient’s native liver biopsy was negative for cirrhosis, but showed evidence of steatosis and bridging fibrosis, suggestive of stage iii fibrosis.

One year later, magnetic resonance imaging of the abdomen showed evidence of a new right lobe lesion adjacent to the surgical bed and consistent with recurrent disease. The patient underwent radiofrequency ablation to the site of recurrence.

At 2 years after the initial diagnosis of hcc, the patient felt a firm mass over his sternum. Computed tomography imaging of his chest showed a 3.4×3.4×4.3 cm soft-tissue mass, with destruction of the upper one third of the sternum. Combined positron-emission and computed tomography imaging showed a destructive sternal mass, avid for fluorodeoxyglucose (fdg) and involving approximately two thirds of the sternum. The region of fdg avidity (maximal standardized uptake value 4) measured 5.8×4.3 cm in the greatest dimension and 9.3 cm craniocaudally [Figure 3(A,B)] and extended to the right pectoralis major muscle. The fdg-avid track extended from the mass along the right internal mammary vein to the proximal portion of the superior vena cava, suggestive of tumour thrombosis. There was no region of focally increased fdg uptake in the liver to indicate new sites of intrahepatic recurrence. That observation was confirmed by magnetic resonance imaging of the abdomen, which again showed no evidence of residual or recurrent hcc. Fine-needle aspiration and core biopsy of the mass were consistent with extrahepatic metastatic hcc [Figure 3(C,D)].
The patient then underwent stereotactic radiation therapy to the right chest wall, with no significant change in the size of the mass. Serum alpha-fetoprotein was 3599 ng/mL (reference: 0.0–8.3 ng/mL); hepatic function and transaminases were normal; and Child–Pugh score was 5 (class A). The patient was started on sorafenib.

After 2 months on sorafenib, the patient underwent image-guided bland embolization of the feeding arteries (left internal mammary artery, then right internal mammary artery). After the bland embolization, serum alpha-fetoprotein showed an initial 50% decline, suggesting response.

Three months after the embolization procedure, repeat imaging showed evidence of enlargement of the sternal mass, with 2 new pulmonary nodules, but without other sites of metastatic disease. Triple-phase CT imaging of the liver continued to show no evidence of recurrent disease, and sorafenib was subsequently discontinued. The patient was then treated with docetaxel and gemcitabine.

After completion of 2 cycles of docetaxel and gemcitabine, the patient developed worsening shortness of breath. Triple-phase liver CT imaging including chest and pelvis revealed evidence of disease progression, with the development of numerous pulmonary nodules and multiple new hypodense round splenic lesions. However, no discrete arterially enhancing liver lesions were seen. On a follow-up visit, the patient was noted to have red nodules along the incision site of the earlier hepatic lobectomy [Figure 4(A)] and the right upper lip. Biopsy of the skin nodules from both sites showed hepatic metastasis to skin [Figure 4(B)]. The patient was started on axitinib, with poor tolerability requiring dose reductions and ultimately discontinuation.

**DISCUSSION**

Hepatocellular adenomas are uncommon benign tumours of the liver that typically occur in women taking oral contraceptive pills. Malignant transformation of HCA into HCC is a rare phenomenon, occurring with reported frequency of 4.2%. In a review of the available literature of HCA in 2010, Stoot et al. identified 19 cases of malignant transformation of HCA, of which only 5 occurred in men.

Other risk factors for malignant transformation include intake of androgens or anabolic steroids, metabolic syndrome, mutation of the beta-catenin gene involved in the Wnt signalling pathway, size greater than 5 cm, and male sex. In one study, the frequency of malignant change was higher in men than in women by a factor of 10. Prolonged corticosteroid therapy has also been reported to produce malignant transformation of a hepatic adenoma in the setting of nephrotic syndrome being treated with 15 years of oral prednisolone.

The exact mechanism and timeline of malignant transformation is unknown, but hepatocyte dysplasia is thought to be the most probable intermediate step, described as the adenoma–carcinoma sequence. In one case, a man developed well-differentiated HCC arising within an adenoma diagnosed 10 years earlier; the HCC was found at the time of surgical removal of the hepatic adenoma.

The malignant transformation in our case was most likely related to beta-catenin mutation. Beta-catenin nuclear staining was positive in few HCA cells, but showed positive in a significantly higher number of HCC cells. A diffuse staining pattern of glutamine synthetase was observed in both the HCA and HCC components. Those findings accord with the World Health Organization classification of beta-catenin–activated HCAs, which reportedly have a higher risk of transformation to HCC.

Another interesting feature of our case is the development of recurrent HCC arising from a HCA after resection of the primary lesion. Of the 19 cases of HCC arising from an HCA reported in the literature, a recurrence was described only in one case, 6 years after resection—a recurrence that was intrahepatic.

Although a hepatectomy, such as the one performed in our patient, is considered curative, the long-term outcome remains less than ideal. The cumulative 5-year recurrence rate after curative hepatectomy was 80% in one study, with the recurrences more frequently being intrahepatic than extrahepatic. Ochiai et al. found that intrahepatic recurrences occurred 90% of the time. However, when extrahepatic metastases occurred, they were indicative of a worse prognosis. Yang et al. found...
that the survival rate for a group of patients with extra hepatic recurrence was 19%; the rate was 61% for those with intrahepatic recurrence.

Extrahepatic hcc metastases most commonly involve lungs, lymph nodes, bones, and adrenal glands. Bone metastasis usually involves vertebrae, ribs, and long bones; multiple sites are common. An increase in the incidence of bone metastasis has been noted in recent times, which can be attributed to improvement in hcc treatment modalities, resulting in improved survival for patients. However, survival data have been described in the English literature. Wu et al. described a case of recurrent hcc presenting as a solitary sternal metastasis in an 81-year-old man who had previously been treated 3 times with radiofrequency ablation. In that patient, abdominal imaging revealed 3 recurrent hepatic tumours, which contrasts with our patient, who had no intrahepatic recurrence at the time that the sternal metastasis was diagnosed.

The prognosis of hcc patients with bone metastasis is poor: median survival is 6.2 months. Our patient survived 23 months after his diagnosis of metastatic hcc, an outcome that could be explained by the absence of intrahepatic hcc recurrence and of underlying cirrhosis.

SUMMARY

Our report documents two rarely reported events occurring in 1 patient: beta-catenin mutation–associated malignant transformation of a HCA, and hcc sternal metastasis without synchronous intrahepatic metastasis. Given the rarity of extrahepatic recurrence without concurrent intrahepatic disease, the optimal management of these patients is unknown. Further cases must be reported, because such reports are imperative for improving treatment and prognosis in these patients.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

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